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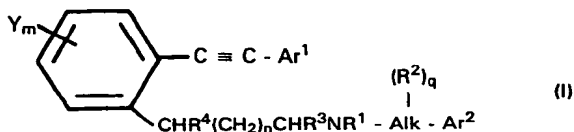
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54 **Aralkyl (arylethynyl) aralkyl amines for use as vasodilators and antihypertensives.**

57 **Acetylenes of the formula (I):**



wherein Y, m, R¹, R², q, Alk, R³, n and R⁴ are as defined herein and Ar¹ and Ar² are aromatic, including the salts and ammonium derivatives of formula (I), in treating angina, hypertension and cardiac arrhythmias. Pharmaceutical compositions, methods of use and synthesis and novel intermediates are also part of the invention.

EP 0 146 271 A2

ACTORUM AG

ARALKYL (ARYLETHYNYL)ARALKYL AMINES FOR USE AS
VASODILATORS AND ANTIHYPERTENSIVES

The present invention comprises various aromatic deriva-
 5 tives of amino acetylenes which are useful as vasodilators
 and in the treatment of hypertension, e.g. in humans.

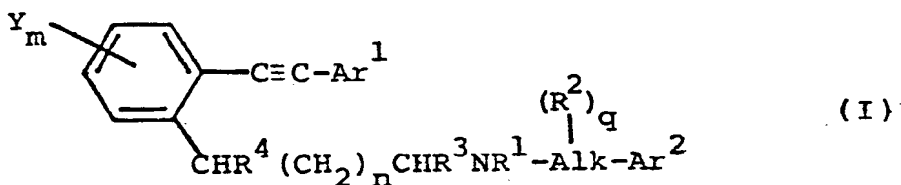
Various phenylethynyl benzylamines are claimed in U.S.
 Patent 3,719,712 and are taught as antiarrhythmic agents.

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Summary of the Invention

Aromatic amino acetylenes of the following formula (I):

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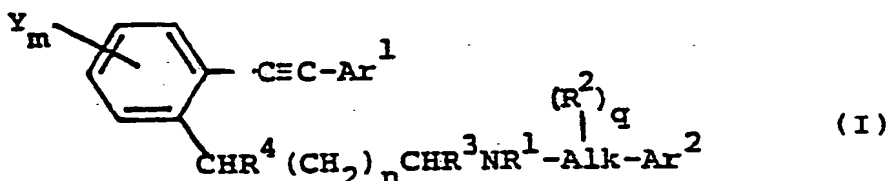
wherein Y , m , R^1 , R^2 , q , Alk , R^3 , n and R^4 are as defined
 herein and Ar^1 and Ar^2 contain aromatic moieties have been
 found to possess vasodilating and anti-hypertensive
 properties when administered to a mammal in need thereof.
 25 Also part of the invention are pharmaceutical compositions
 containing compounds of the formula (I) and methods of
 treatment using such compositions.

30

Detailed Description of the Invention

Compounds of the invention are of the following formula
 (I):

35



-2-

wherein

5 Y is independently alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyloxy, alkanoylamino, amino, monoalkylamino, dialkylamino, hydroxy, halogen or cyano or methylenedioxy or ethylenedioxy at adjacent ring carbons;

10 m is 0, 1, 2 or 3;

15 Ar¹ is phenyl or a 5- or 6-membered heterocyclic aromatic ring which rings may be independently substituted by one or more of alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino, dialkylamino, carboxamido, halogen, fluoroalkyl or cyano;

20 R¹ is hydrogen, alkyl, hydroxyalkyl, cycloalkyl or cycloalkylalkyl or R¹ is independently selected from the group consisting of the defined values of -Alk-Ar²;

R² is independently hydroxy, alkyl or phenyl;

25 Alk is a straight chain alkylene of about 1 to 4 carbons;

30 q is 0, 1 or 2 or 3 if Alk is alkylene of about 2 to 4 carbons;

35 Ar² is a phenyl, phenoxy, thiophenoxy, naphthyl or a 5- or 6-membered heterocyclic aromatic ring which rings may be substituted independently by one or more of alkyl, alkoxy, alkylthio, hydroxy, halogen, fluoroalkyl, nitro, amino or dialkylamino or by methylenedioxy at adjacent ring carbons;

R^3 is hydrogen, alkyl or alkoxyalkyl;

n is 0, 1 or 2; and

5 R^4 is hydrogen or alkyl,

provided that the hydroxy of the hydroxyalkyl for R^1 and the hydroxy for R^2 are not attached to the same carbon as the nitrogen atom in formula (I), and the pharmaceutically
10 acceptable acid addition salts and quaternary ammonium compounds thereof.

In particular, Y is alkyl of about 1 to 6 carbons such as methyl or ethyl; alkoxy of about 1 to 6 carbon atoms such
15 as methoxy or ethoxy; alkylthio of about 1 to 6 carbons such as methylthio; alkylsulfinyl of about 1 to 6 carbons such as methylsulfinyl; alkylsulfonyl of about 1 to 6 carbons such as methylsulfonyl; alkanoyloxy of about 2 to 6 carbons such as acetoxy; alkanoylamino of about 2 to 6
20 carbons such as acetylamino; amino; monoalkylamino of about 1 to 6 carbons such as ethylamino; dialkylamino of about 2 to 12 carbons such as dimethylamino; hydroxy; halogen such as fluoro, chloro or bromo; cyano; or methylenedioxy or ethylenedioxy wherein the two oxygen
25 atoms are attached to two adjacent carbons of the benzene ring. Although the Y groups may be attached at any of the 4 open positions of the benzene ring, particularly preferred are compounds wherein the Y groups are attached at the 4- and/or 5-positions of the ring relative to the
30 amino side chain with the acetylene moiety being at the 2-position.

Ar^1 is phenyl or a 5- or 6-membered heterocyclic aromatic ring containing 1, 2 or 3 heteroatoms such as nitrogen,
35 sulphur or oxygen with specific examples being thiophene, pyrrole, furan, pyrazole, imidazole, triazole, oxazole,

thiazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine or triazine. Such heterocycles may be attached via a ring carbon atom to the acetylene moiety. The optional substitution on the Ar¹ ring is one or more, same or different, of alkyl, alkoxy or alkylthio of about 1 to 6 carbons, such as methyl, ethyl, methoxy, iso-propoxy or methylthio; alkylsulfinyl or alkylsulfonyl of about 1 to 6 carbons such as methylsulfinyl; amino; alkylamino of about 1 to 6 carbons such as methylamino or isopropylamino; dialkylamino of about 2 to 12 carbons, e.g., of about 1 to 6 carbons in each alkyl group, such as dimethylamino or N-ethyl-N-n-propylamino; carboxamido of the formula -CONH₂; halogen such as fluoro, chloro, or bromo; fluoroalkyl of about 1 to 6 carbons and one or more fluoro atoms with examples being 2,2,2-trifluoroethyl and trifluoromethyl; or cyano. Such optional substituents may be attached at any available site on the phenyl or heterocyclic ring, in particular at the meta and para positions of a phenyl ring relative to the acetylene.

R¹ is hydrogen; alkyl of about 1 to 6 carbons such as methyl, ethyl or iso-propyl; hydroxyalkyl of about 1 to 6 carbons such as 2-hydroxyethyl; cycloalkyl of about 3 to 6 carbons such as cyclopropyl or cyclohexyl; or cycloalkyl-alkyl of about 4 to 7 carbons such as cyclopropylmethyl or R¹ is independently, i.e., independent of the value for -Alk-Ar² chosen for these symbols in formula (I), selected from the group consisting of the defined values of -Alk-Ar², i.e., the entire list of possible -Alk- values and -Ar² values. For example, R¹ can be phenethyl, i.e., R¹ is -Alk-Ar² where Alk is ethylene and Ar² is phenyl.

R² is independently hydroxy; alkyl of about 1 to 4 carbons such as methyl, ethyl or iso-propyl; or phenyl.

Alk is methylene, ethylene, trimethylene or tetramethylene.

q is 0, 1, 2 or 3, in particular 0, 1 or 2.

5

Ar² is phenyl; phenoxy; thiophenoxy; naphthyl, e.g., 1- or 2-naphthyl; or a 5- or 6-membered heterocyclic aromatic ring, preferably one having 1 heteroatom such as nitrogen, sulfur or oxygen, e.g. furan or thiophene attached at the 2 or 3 position, pyrrole attached at the 1, 2 or 3 position and pyridine attached at the 2, 3 or 4 position. The open positions of the ring, or rings in the case of naphthyl, of Ar² may be substituted by one or more, e.g. one or two, same or different, of alkyl of about 1 to 6 carbons such as methyl or ethyl; alkoxy of about 1 to 6 carbons such as methoxy and ethoxy; alkylthio of about 1 to 6 carbons such as methylthio; hydroxy; halogen such as fluoro, chloro and bromo; fluoroalkyl of about 1 to 6 carbons and one or more fluorine atoms with examples being 2,2,2-trifluoroethyl and trifluoromethyl; nitro; amino; or dialkylamino of about 2 to 12 carbons such as dimethylamino; or methylenedioxy at adjacent ring carbons particularly if Ar² is phenyl, phenoxy or thiophenoxy, e.g., 3,4-methylenedioxyphenyl.

25

R³ is hydrogen; alkyl of about 1 to 6 carbons such as methyl, ethyl, iso-propyl and n-pentyl; or alkoxyalkyl of about 1 to 6 carbons in each alkyl portion such as methoxymethyl, n-butoxymethyl and ethoxyethyl.

30

R⁴ is in particular, hydrogen; or alkyl of about 1 to 6 carbons with examples being methyl, ethyl and n-butyl.

The pharmaceutically acceptable acid-addition salts of the compounds of formula (I) include those of a mineral or

35

organic acid such as hydrochloric, hydrobromic, hydro-
iodic, sulfuric, phosphoric, fumaric, maleic, cyclohexyl-
sulfamic, citric, lactic, methanesulfonic and similar
acids. The term "independently" is used with respect to
5 Y, Ar¹ substitution, R² and Ar² substitution to indicate
that when more than one of such substitution is possible,
e.g., when q and m are 2 or 3, such substitution may be
different from each other, e.g., when q is 2, one such R²
may be -OH and the other -CH₃.

10

The quaternary ammonium compounds of the compounds of
formula (I) include those formed with an alkylhalide or
sulfate of about 1 to 6 carbons, e.g., an alkyl bromide or
iodide such as methyl iodide. The salts and ammonium
15 compounds may be prepared by conventional techniques.

Compounds of Formula (I) and other compounds of the
invention may exist in various isomeric forms, e.g., in
view of the presence of an asymmetric carbon. It is
20 understood that the present invention includes all such
individual isomers and their racemates. Also within the
scope of the invention are compounds of the invention in
the form of hydrates and other solvate forms.

25 Particular compounds of the invention may be defined as
those of formula (I) having one or more of the following
definitions: Y is alkoxy, particularly methoxy; m is 0 or
1 and the Y group is at the 5 position of the ring with
the aminoalkyl and the acetylene moieties at the 1 and 2
30 positions, respectively; Ar¹ is phenyl or phenyl
substituted with a single substituent such as chloro; R¹
is hydrogen or alkyl such as methyl; R² is methyl; q is 0
or 1; Alk is methylene or ethylene; Ar² is phenyl or
phenyl with one or two substituents such as alkoxy, e.g.,
35 methoxy, or chloro; R³ is hydrogen or methyl; n is 0 or 1;
and R⁴ is hydrogen.

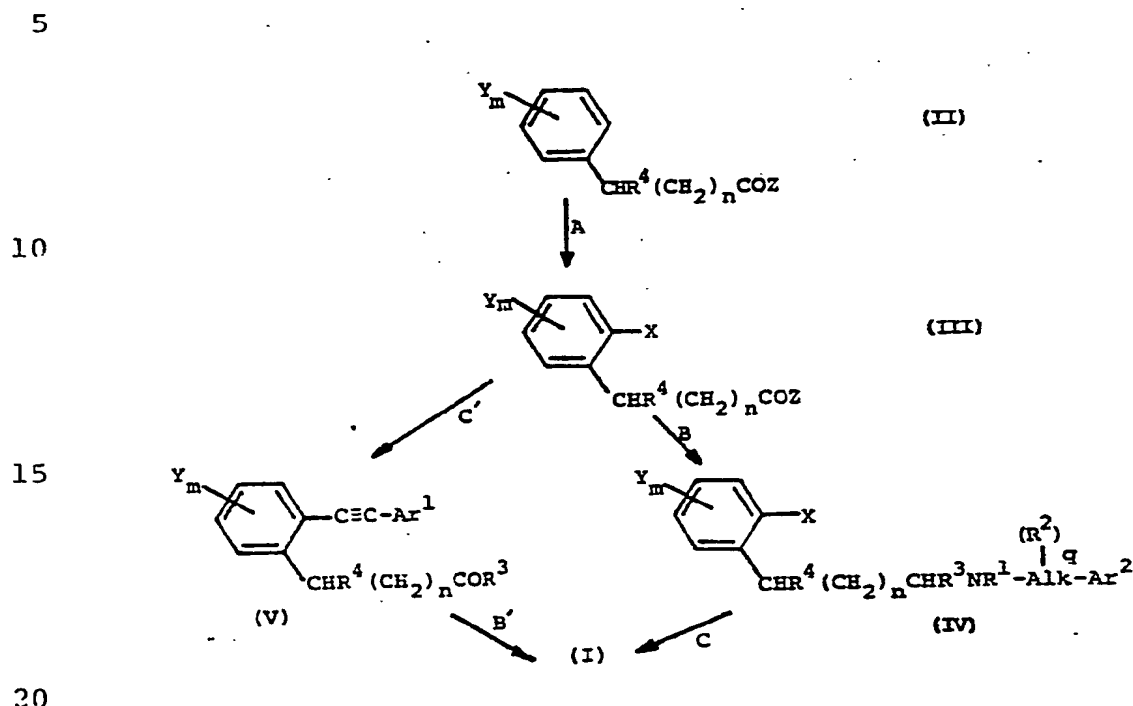
Preferred compounds are of the formula (I) wherein

- 5 i) Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is methyl; q is 0; Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; R³ is methyl; n is 1; and R⁴ is hydrogen; or
- 10 ii) Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is methyl; q is 0; Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; R³ is hydrogen; n is 0; and R⁴ is hydrogen; or
- 15 iii) Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is hydrogen; q is 0; Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; n is 0; and R⁴ is hydrogen; or
- 20 iv) Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is methyl; q is 0; Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; R³ is methyl; n is 0, and R⁴ is hydrogen; or
- 25 v) Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is hydrogen; q is 0; Alk is ethylene; Ar² is 3,4-dichlorophenyl; n is 0; and R⁴ is hydrogen; or
- 30 vi) Y is methoxy at the position para to the acetylene; m is 1; Ar² is phenyl; R¹ is methyl; q is 0; Alk is ethylene; Ar² is 3,4-dichlorophenyl; R³ is hydrogen; n is 0; and R⁴ is hydrogen.

35 Unless otherwise noted, "alkyl" in the present specification, e.g., as part of an alkoxy group, is indicative of a straight or branched chain group.

Compounds of formula (I) may be prepared according to the following Reaction Scheme I:

Reaction Scheme I:



Three primary stages are used in the preparation of compounds of the formula (I) by starting with arylalkanoic acids or arylalkanones of the formula (II) wherein Z is OH or R^3 , e.g., hydrogen, alkyl or alkoxyalkyl. The stages are halogenation, construction of an amine functionality and condensation with an Ar^1 -acetylene. In the halogenation stage A, wherein X is a halogen such as Br or I, the aryl ring of (II) is halogenated in the position ortho to the eventual aminoalkyl side chain. Brominations may be carried out with bromine in halocarbon solvents or acetic acid at temperatures from about -20 to 80°C and may be conducted in the presence of a Lewis acid catalyst such as ferric chloride. Iodinations may be carried out using ICl or INO_3 in halocarbon solvents or acetic acid over a

range of room temperature to about 100°C. Iodinations may be carried out using iodine in the presence of an iodide scavenger such as silver acetate, silver sulfate, mercuric oxide or nitric acid. For reactive substrates, iodine may be used alone or in conjunction with a mild base such as sodium bicarbonate. Alternatively, the halogenation may be accomplished by mercuriation, e.g., with HgCl_2 or thallation, e.g., with $\text{Tl}(\text{O}_2\text{CCF}_3)_3$, followed by treatment with iodide or bromide as described by A. McKillop, et al. in J. Am. Chem. Soc., 93, 4841 (1971).

In stage B or B' the desired amine function is constructed. In a first embodiment for Stage B and if R^3 is to be hydrogen, a compound of formula (III) wherein Z is OH may be converted to the corresponding acid chloride by reagents such as oxalyl chloride, thionyl chloride or phosphoryl chloride. The reaction may be carried out at room temperature to about 100°C in an aprotic, nonpolar solvent such as toluene, chloroform or methylene chloride or the reaction may be carried out neat. The preferred method employs oxalyl chloride in toluene in the presence of DMF. The acid chloride is converted to the corresponding amide of formula (III) wherein Z is $\text{NR}^1\text{-Alk}(\text{R}^2)_q\text{-Ar}^2$. This conversion may be carried out by treatment of the acid chloride with an excess of amine of the formula $\text{R}^1\text{NH-Alk}(\text{R}^2)_q\text{-Ar}^2$, for instance in toluene or a halocarbon solvent at temperatures from -30°C to 45°C. Alternatively, slightly more than one equivalent of amine may be used in the presence of an auxillary base such as triethylamine, pyridine, sodium hydroxide or potassium carbonate. The amide is then reduced to the corresponding amine of the formula (IV) wherein R^3 is hydrogen to complete elaboration of the amine function. The reduction of the amide is preferably carried out with an excess of borane in THF at the reflux temperature of the solvent. The excess borane is decomposed by addition of water and

the amine borane complex is decomposed by heating in the presence of an alkanolic acid, preferably propionic acid, a mineral acid or an alkali metal hydroxide to give the amine of formula (IV) wherein R^3 is hydrogen. Alternatively, the amide may be reduced with lithium aluminum hydride, sodium borohydride plus aluminum chloride or sodium borohydride in acetic or trifluoroacetic acid. A second embodiment for the construction of the amine function consists of reductive alkylation of amines of the formula $R^1NH-Alk(R^2)_q-Ar^2$ by aldehydes or ketones of the formulae (III) or (V) wherein Z is R^3 , i.e., hydrogen, alkyl or alkoxyalkyl. The reductive alkylation may be carried out in one step from the carbonyl compound and the amine using sodium cyanoborohydride as the reducing agent in a lower alkanol or acetonitrile as the solvent at neutral to mildly acidic pH at temperatures from 0 to 40°C. Hydrogenation over a noble metal catalyst may also be used to bring about the reduction. Reductive alkylation may also be carried out in two steps. The carbonyl compound and amine are first converted to an imine or iminium salt by treatment with molecular sieves or azeotropic removal of water. Reduction is then effected by $NaBH_4$, $NaCNBH_3$ or catalytic reduction. Using the two step reductive alkylation, the alkyl groups R^1 and $-Alk(R^2)_q-Ar^2$ may be attached sequentially. In stage B', the reductive alkylation cannot be carried out by catalytic hydrogenation in view of the possibility of hydrogenation of the acetylene moiety.

If R^1 is to be methyl, the Eschweiler-Clark procedure using formaldehyde as the carbonyl compound and formic acid or sodium cyanoborohydride as the reducing agent is used.

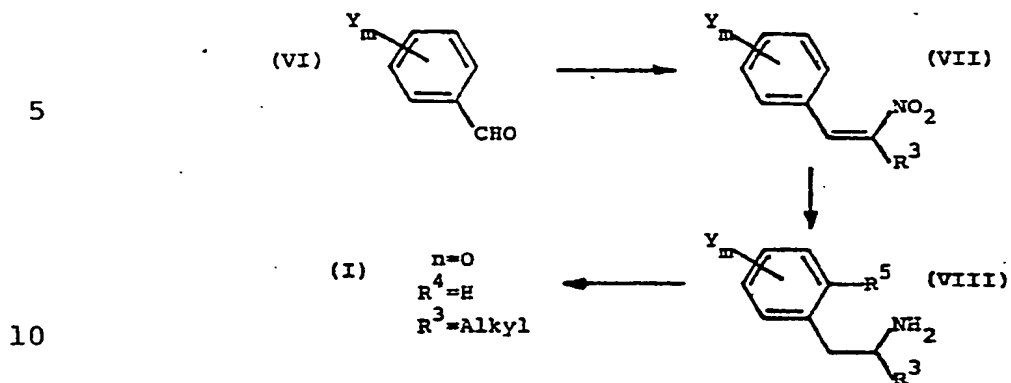
The third stage in Reaction Scheme I is the replacement of halide X by an Ar^1 -acetylene and is labeled C and C'. For

stage C, the transformation may be carried out by heating the aryl halide (IV) with a cuprous Ar^1 -acetylide at the reflux temperature of the solvent, preferably pyridine or DMF as described by R. D. Stephens, et al. in

- 5 J. Org. Chem., 28, 3313 (1963). Secondly, the coupling of the arylhalides (III) or (IV) with an Ar^1 -acetylene may be accomplished by treating the arylhalide with chlorozinc Ar^1 -acetylide in the presence of a palladium or nickel catalyst, preferably $\text{Pd}[(\text{Ph}_3)\text{P}]_4$ in an etherial solvent
- 10 such as THF at -30°C to ambient temperature, as described by A. O. King et al. in J. Org. Chem., 43, 358 (1978). Thirdly, coupling may be by treating the arylhalide (III) or (IV) with the Ar^1 -acetylene and catalytic quantities, e.g., 0.5 to 10 mole percent, of $\text{Pd}[(\text{Ph}_3)\text{P}]_4$,
- 15 $\text{Pd}(\text{OAc})_2[\text{P}(\text{Ph})_3]_2$ or $\text{PdCl}_2[\text{P}(\text{Ph})_3]_2$ in an amine solvent such as diethylamine, piperidine, pyrrolidine or triethylamine at ambient temperature to the reflux temperature of the solvent in the presence or absence of cuprous iodide as described by K. Sonogashira et al. in Tetrahedron
- 20 Letters, 4467 (1975) or H.A. Dieck et al. in J. Organometal. Chem. 93, 253 (1975). When R^1 is to be hydrogen, the method of Stephens et al. may not be used. The stages of reaction Scheme I may be carried out in the sequence A, B and C or the sequence A, C' and B'. When R^1
- 25 is to be alkyl, such may be attached by reductive alkylation after carrying out stage C or B'.

A second general method for preparation of compounds of formula (I) where n is 0, R^4 is H and R^3 is alkyl is shown

30 in Reaction Scheme II:

Reaction Scheme II

An aromatic aldehyde (VI) is condensed with a nitroalkane of the formula $R^3CH_2NO_2$ to afford a nitroolefin (VII). Condensation of the nitroalkane with the aromatic aldehyde is carried out using ammonium acetate or a primary alkylamine as catalyst in, for example, glacial acetic acid, ethanol or toluene as the solvent at ambient to elevated temperatures preferably at the reflux temperature of the solvent. The nitroolefin (VII) is then reduced to an amine (VIII) where R^5 is hydrogen with lithium aluminum hydride in an ether solvent, or by catalytic reduction over Raney nickel or a noble metal catalyst. The amine (VIII) is halogenated on the aromatic ring using the methods described for Stage A to afford a halogenated amine of the formula (VIII) where R^5 is halo. The halo-amine is coupled with an Ar^1 -acetylene using the procedure of King et al. or Sonogashiri et al. as described for Stage C to give an acetylene of formula (VIII) where R^5 is $-C\equiv C-Ar^1$. Attachment of the groups $-Alk(R^2)_q-Ar^2$ and/or R^1 by reductive alkylation starting with the appropriate carbonyl compounds, e.g., CH_3CHO to have ethyl as the R^1 moiety or benzaldehyde to give benzyl as the $-Alk(R^2)_q-Ar^2$ moiety, affords the product of the formula (I) wherein n is 0, R^4 is hydrogen and R^3 is alkyl.

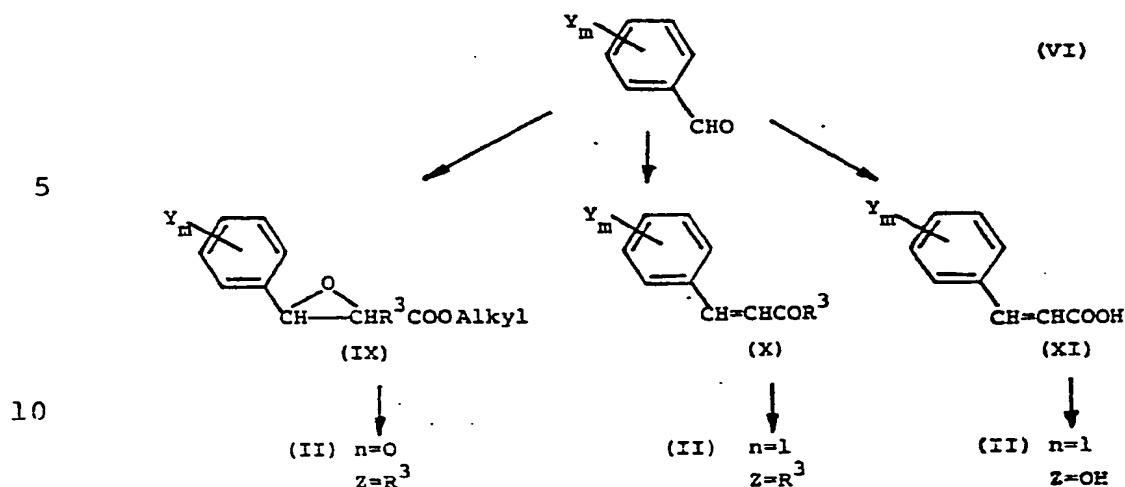
Starting materials for Reaction Schemes I and II are widely known. However, starting materials with particular substituents may be synthesized by the following methods:

- 5 First, alkanones of the formula (II) wherein Z is R^3 , n is 0 and R^4 is hydrogen may be prepared by condensation of an aromatic aldehyde (VI) with an alpha-haloester, e.g. of the formula $R^3CHBrCOOAlkyl$ in the presence of an alkali metal alkoxide to give a glycidic ester of the formula
10 (IX). Hydrolysis with an alkali metal hydroxide followed by thermal decarboxylation affords the arylalkanone (II) wherein Z is R^3 , n is 0 and R^4 is hydrogen. Conversion of such a (II) compound to one wherein R^4 is alkyl may be carried out by alkylation of an alkali metal enolate of
15 the carbonyl compound (II) with a reagent such as ethyl iodide.

- Second, arylalkanones of the formula (II) where Z is R^3 , n is 1 and R^4 is hydrogen may be prepared by a Claisen-Schmidt condensation of a methyl ketone, CH_3COR^3 with an
20 aromatic aldehyde (VI) in the presence of an alkali metal hydroxide followed by hydrogenation of the alpha,beta-unsaturated ketone (X) over a noble metal catalyst.

- Third, arylalkanoic acids of the formula (II) wherein Z is
25 OH, R^4 is hydrogen and n is 1 may be prepared by Knoevenagel condensation of an aromatic aldehyde (VI) with malonic acid followed by hydrogenation of the resulting cinnamic acid (XI) over a noble metal catalyst:

-14-



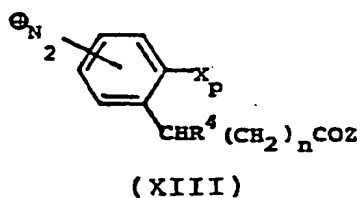
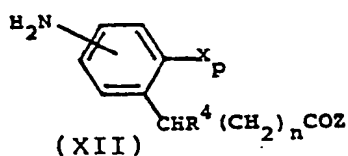
15 In each of the above three sequences, the aromatic aldehyde may be one with an X group ortho to the CHO and such a starting material will result in final products of the formula (III) after the steps described above.

20 For the preparation of intermediates (II) and (III) where Y is halo, alkylthio, hydroxy, cyano or dialkylamino, the corresponding compounds (XII) where p is 0 or 1, respectively, may be utilized as starting materials. The amine (XII) may be diazotized to give (XIII) and the diazonium group may be treated with CuCl, CuBr or CuCN to yield (II) or (III) wherein Y is Cl, Br or CN, respectively.

25 Pyrolysis of the diazonium fluoroborate or hexafluoro phosphate gives the corresponding aryl fluoride. Hydrolysis of the diazonium salt would lead to the corresponding phenol. Treatment of the diazonium salt successively with potassium ethyl xanthate, base and an alkyl halide leads to the alkylthio product. Reductive alkylation of the amino compound (XII) with formaldehyde or an alkanal and sodium cyanoborohydride gives rise to intermediates (II) or (III) bearing the dialkylamino group.

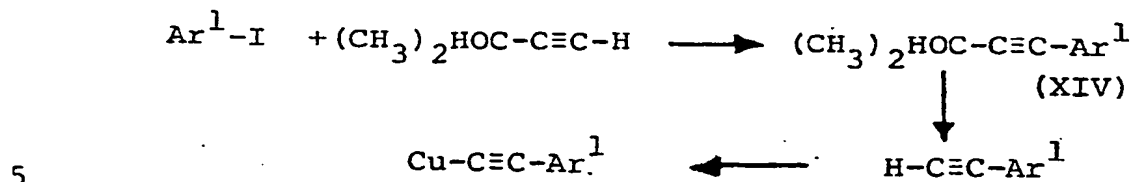
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The various Y groups in compounds such as those of formulae (II), (III), (IV) and (XII) may be transformed among each other by techniques known in the art. For example, when Y is amino, the corresponding compound wherein Y is monoalkylamino may be prepared by acylation with an acyl halide or anhydride to yield the corresponding compound where Y is alkanoylamino followed by hydride reduction with borane or lithium aluminum hydride. When Y is alkylthio the corresponding compound where Y is alkylsulfinyl or alkylsulfonyl may be produced by oxidation with hydrogen peroxide or a peracid such as trifluoroperacetic acid known in the art. Variation in the reaction temperature, reaction time and reactivity of the substrate and particular reagent will all be factors influencing whether the product is the sulfinyl or sulfonyl and manipulation of such variables is well known in the art. When Y is alkoxy, the corresponding compound wherein Y is hydroxy may be produced by conventional dealkylating reagents such as boron tribromide, boron trichloride, trimethylsilyl iodide and hydrogen iodide. In addition, compounds wherein Y is alkoxy may be produced from the phenol by alkylation with a reagent such as alkyl halide, e.g., methyl iodide, in the presence of a base.

Ar¹-acetylenes as required may be prepared by the method of Ames et al as described in Synthesis, 364 (1981). Treatment of Ar¹ iodides of the formula Ar¹-I with PdCl₂[(Ph)₃P]₂ or Pd(OAc)₂[(Ph)₃P]₂ and 2-methyl-3-butyne-2-ol affords acetylenic carbinols (XIV). Cleavage of the carbinol (XIV) with an alkali metal hydroxide gives rise to the Ar¹-acetylenes. The Ar¹-acetylenes may be converted to cuprous Ar¹-acetylides by treatment with cuprous iodide in ammonium hydroxide solution.



Compounds of the formula (I), including the acid-addition salts and quaternary compounds thereof, are calcium blockers and as such, are effective against angina, hypertension and cardiac arrhythmias in mammals, particularly as described by S.F. Flaim et al. in "Calcium Blockers - Mechanisms of Action and Clinical Applications", Urban and Schwarzenberg, Baltimore, Md. (1982). Techniques used to determine efficacy as a calcium blocker are described by S.F. Flaim et al. in Pharmacology, Vol. 22, p. 286 to 293 (1981). Compounds of the invention have the advantage of a significant separation between the desirable coronary vasodilator effects and the less desirable side effect of decreased myocardial contractile force.

The activity of compounds of formula (I) for the treatment of hypertension was determined using the Spontaneously Hypertensive Rat (SHR) test as described below.

In this test, the arterial pressure of adult spontaneously hypertensive rats (Charles River) is monitored directly via an aortic cannula. The SH rats are anesthetized with an inhalation anesthetic (ether). The left carotid artery is isolated and cannulated. The tip of the cannula is advanced to the aorta and the cannula is exteriorized behind the neck at the level of the scapula. Animals are placed in individual cages and allowed to recover from the anesthetic and are kept unrestrained. The arterial cannula is connected to the pressure transducer which is attached to the recorder. The test compounds are administered to at least 3 rats at doses selected in the range of

0.1 to 100 mg/kg of body weight by intraperitoneal (i.p.) or oral (p.o.) routes of administration. The arterial pressure and heart rate are monitored for a minimum of 24 hours. A test compound is considered to be active as an antihypertensive agent if the mean arterial pressure (MAP) indicates a fall of >15 mm of Hg. Each animal serves as its own control.

The results of this test for compounds of formula (I), expressed as "Max Fall BP" (Maximum Fall in Mean Arterial Pressure) are shown in Table I.

In addition to their utility in the treatment of hypertension, the compounds of formula (I) are useful in the treatment of the symptoms of angina pectoris by virtue of their ability to dilate coronary arteries. Their activity was measured using the "Langendorff's isolated heart" preparation. This test has been described in "Pharmacological Experiments on Isolated Preparations", Staff of the Department of Pharmacology, University of Edinburgh, 2nd Ed., Churchill Livingstone, N.Y., 1970, pp. 112-119. The test compounds were administered at concentrations of 3000, 1000, 300, 100, 30, 10, 3, 1 and 0.3 nanomolar (10^{-9} molar).

The minimum concentration (EC_{30}) needed to elicit a 30 percent increase in coronary flow is shown in Table I for compounds of the formula (I) wherein Y is methoxy at the position para to the acetylene; m is 1; n is 0 except in the results for Example 32 where n is 1; Ar^1 is phenyl; q is 0; Alk is ethylene; and R^4 is hydrogen.

TABLE I

Example Number ^a	R ¹	R ³	Ar ²	Max Fall (dose ^c)	BP ^b (x10 ⁻⁹ M)	EC ₃₀ (x10 ⁻⁹ M)
5	32	CH ₃	CH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃	40 (30)	30
	39	CH ₃	H	3,4-(CH ₃ O) ₂ C ₆ H ₃	70 (30)	10
	33	H	CH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃	67 (30)	10
	40	CH ₃	CH ₃	3,4-(CH ₃ O) ₂ C ₆ H ₃	77 (3)	10
	33	H	CH ₃	3,4-Cl ₂ C ₆ H ₃	43 (3)	0.1
10	40	CH ₃	CH ₃	3,4-Cl ₂ C ₆ H ₃	84 (3)	0.3

a) All test results were for the fumarate salt except Example 32 which was the hydrochloride

15 b) in mm of Hg

c) in mg/kg of body weight

For the treatment of hypertension or angina, compounds of the present invention of the formula (I) may be administered orally or parenterally in a pharmaceutical composition comprising about 1 to 2,000 mg, preferably about 30 to 200 mg of one or more of the acetylene compounds per day for an average adult human depending on the activity of the particular compound chosen. The dosage may be divided into 1 to 4 unit dosage forms per day. While the therapeutic methods of the invention are most useful for human subjects in need of alleviation of hypertension or angina, the compounds may be administered to other mammals at comparable dosages per weight of the subject.

Pharmaceutical compositions containing the acetylene compounds of the present invention of formula (I), an acid addition salt thereof or a quaternary ammonium compound thereof as the active ingredient may be prepared by intimately mixing the acetylene compound with a pharmaceutical

carrier according to conventional pharmaceutical compound-
ing techniques, which carrier may take a wide variety of
forms depending on the form of preparation desired for
administration, e.g., oral or parenteral. In preparing
5 the compositions in oral dosage form, any of the usual
pharmaceutical media may be employed, including liquid
carriers such as water, glycols, oils, alcohols and the
like for oral liquid preparations such as suspensions,
elixirs and solutions; and solid carriers such as
10 starches, sugars, kaolin, calcium stearate, ethyl cellu-
lose, etc., including materials which function as lubri-
cants, binders, disintegrating agents and the like for
powders, capsules and tablets. Because of their ease in
administration, tablets and capsules represent the most
15 advantageous oral dosage form. These compositions employ
solid pharmaceutical carriers such as the aforementioned
starches, sugars, kaolin and the like, generally with a
lubricant such as calcium stearate. It is especially
advantageous to formulate the aforementioned pharmaceu-
20 tical compositions in dosage unit form for ease of
administration and uniformity of dosage. The term "dosage
unit form" as used in the specification and claims herein
refers to physically discrete units suitable as unitary
dosages, each unit containing a predetermined quantity of
25 active ingredient calculated to produce the desired
therapeutic effect in association with the required
pharmaceutical carrier. Examples of such dosage unit
forms are tablets, capsules, pills, powder packets,
wafers, teaspoonful, tablespoonful and the like, and
30 segregated multiples thereof.

Also part of the present invention are novel intermedi-
ates, e.g., of the formula (II).

35 In the following Examples, the following abbreviations are
used: E (trans); Z (cis); bp (boiling point); mp (melting

point); g (grams); ml (milliliters); glc (gas liquid chromatography); NMR (nuclear magnetic resonance); J (coupling constant); d (doublet); dd (double doublet); s (singlet); m (multiplet); t (triplet); N (normal); M (molar); THF (tetrahydrofuran); MeOH (methanol); DMF (dimethylformamide); mmoles (millimoles); mg (milligrams); mm (millimeters); hr (hours); min. (minutes); and C, H, N, etc. (the chemical symbols for the elements). Unless otherwise indicated, all temperatures are reported in degrees centigrade ($^{\circ}\text{C}$), all pressures in mm of mercury and all references to ether are to diethyl ether.

Example 1

15 2-Iodo-5-methoxybenzeneacetic Acid

A solution of 45 g (0.27 mole) of 3-methoxybenzeneacetic acid, 52.6 g (0.32 mole) of iodine monochloride and 1 g of iodine was allowed to stand in 500 ml of glacial acetic acid for six days at room temperature. The reaction was poured into water and the solid collected. It was recrystallized from toluene to give 51 g of crystalline 2-iodo-5-methoxybenzeneacetic acid, mp $133.5\text{--}134.5^{\circ}\text{C}$ (65% yield).

25 Example 2

2-Iodo-5-methoxybenzenepropanoic Acid

Samples of iodine (138.6 g, 0.759 mole) and silver acetate (126.7 g, 0.759 mole) were added in portions over 20 min to a solution of 138.6 g (0.759 mole) of 3-methoxybenzenepropanoic acid in 750 ml glacial acetic acid. An additional 250 ml of glacial acetic acid was added. The mixture became warm and was stirred for one hour. The precipitated silver iodide was filtered and washed with acetic acid and the filtrate was poured into ice water and the solid collected. The solid was taken up in ether,

washed with sodium thiosulfate solution and brine, dried with MgSO_4 and the solvent evaporated in vacuo. The residue was recrystallized from CHCl_3 /ligroin to give 148.7 (64% yield) of 2-iodo-5-methoxybenzenepropanoic acid, mp 105-106°C.

Example 3

2-Iodo-5-methoxy- α -methylbenzeneethanamine hydrochloride

Samples of iodine (49.7 g, 0.196 mole) and silver acetate (32.7 g, 0.196 mole) were added in portions to a solution of 29.4 g (0.178 mole) of 3-methoxy- α -methylbenzeneethanamine in 473 ml of glacial acetic acid. The mixture was stirred for one hour. The acetic acid was evaporated in vacuo. The residue was partitioned between ether and sodium hydroxide solution. The ether layer was washed with water and brine and dried with K_2CO_3 . The solvent was evaporated in vacuo to give 45.4 g of an oil. The hydrochloride was prepared from ethereal hydrogen chloride and recrystallized from CH_3CN to give 35.7 g of 2-iodo-5-methoxy- α -methylbenzeneethanamine hydrochloride, mp 194-196°C.

Example 4

1-(2-Iodo-5-methoxyphenyl)butane-3-one

Samples of iodine (42.4 g, 0.167 mole) and silver acetate (27.87 g, 0.167 mole) were added in portions to a solution of 29.8 g (0.167 mole) of 1-(3-methoxyphenyl)butane-3-one in 167 ml of glacial acetic acid. The mixture was stirred one hour. The silver iodide was removed by filtration and washed with acetic acid. The filtrate was partitioned between ether and water. The ether layer was washed with water, sodium bicarbonate

solution and sodium thiosulfate solution. The ether solution was dried with MgSO_4 and evaporated to dryness in vacuo. There was obtained 41.8 g (82% yield) of oily 1-(2-iodo-5-methoxyphenyl)butane-3-one.

5

^1H NMR (CDCl_3): 7.5-7.8 (d, $J=9$, 1H); 6.75-6.9 (d, $J=3$, 1H); 6.3-6.65 (dd, $J=3$, 10, 1H); 3.7-4.0 (s, 3H); 2.5-3.1 (m, 4H); 2.2 (s, 3H).

10 Example 5

Using the procedure of Example 4 and substituting the appropriate ketone for 1-(3-methoxyphenyl)butane-3-one the following products were obtained respectively:

15

(2-iodo-5-methoxyphenyl)-2-propanone, mp 57-58°
1-(2-iodo-5-methoxyphenyl)octan-3-one

Example 6

20

2-Iodo-5-methoxybenzenepropanoyl chloride

To a solution of 13.0 g (0.042 mole) of 2-iodo-5-methoxybenzenepropanoic acid and 4 ml of DMF in 90 ml of dry
25 toluene at 0°C was added 4.00 ml (0.046 mole) of oxalyl chloride over 15 min. The reaction was stirred overnight to give a solution 2-iodo-5-methoxybenzenepropanoyl chloride in toluene.

30 Example 7

By employing the appropriate starting materials and following the procedure of foregoing Example 6, the following intermediate acid chlorides were prepared:

35

2-Iodo-5-methoxybenzeneacetyl chloride
2-Iodo-5-methylthiobenzenepropanoyl chloride
5-Fluoro-2-iodobenzenepropanoyl chloride

Example 8N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamide

5 A solution of 13.8 g (0.042 mole) of 2-iodo-5-methoxybenzenepropanoyl chloride in 80 ml of toluene was cooled to 0°C and 24.6 g (0.126 mole) of N-methylhomoveratrylamine was added over a 15-minute period. An additional 50 ml of
10 toluene was added. The temperature was allowed to warm to room temperature and stirring continued for 3-1/2 hours. The mixture was partitioned between 500 ml of methylene chloride and 400 ml of water. The methylene chloride layer was separated and washed with 400 ml of 5%
15 hydrochloric acid followed by a washing with 400 ml of 5% sodium hydroxide solution. The organic phase was dried over anhydrous magnesium sulfate and evaporated in vacuo to yield N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamide, a pale yellow oil that
20 partially crystallized on standing.

Example 9

25 Following the procedure of Example 8 and employing equivalent quantities of the appropriate acid chloride in place of 2-iodo-5-methoxybenzenepropanoyl chloride and the appropriate amine in place of N-methylhomoveratrylamine the following amides were obtained as products respectively:

30 N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodobenzeneacetamide, mp 163-164°C
2-Iodo-5-methoxy-N-(2-phenylethyl)benzenepropanamide, mp 131-132°C
N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodo-N-methyl-5-methylthiobenzenepropanamide (oil)
35 N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-fluoro-2-iodo-N-methylbenzenepropanamide (oil)

Example 10N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamine 4-Methylbenzene Sulfonate

- 5 A slurry of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamide in 180 ml of THF was added over a 15-minute period to 126 ml (0.126 mole) of 1 M $\text{BH}_3 \cdot \text{THF}$ solution under N_2 . The mixture was heated
- 10 to reflux for two hours. The reaction mixture was cooled in an ice/water bath and quenched by addition of a mixture of 25 ml of water and 25 ml THF. The solvents were evaporated in vacuo, the residue treated with 50 ml of propionic acid and heated to reflux for 1-1/2 hours.
- 15 After cooling to room temperature, the mixture was partitioned between 600 ml of water and 400 ml of ether. The pH was adjusted to pH 8 by addition of 50% sodium hydroxide solution. The aqueous phase was separated and further basified with sodium hydroxide to pH 12 followed
- 20 by extraction with 200 ml of ether. The combined ether extracts were washed with two 500 ml portions of 10% sodium hydroxide solution and dried over anhydrous potassium carbonate. The solvent was removed in vacuo to yield a colorless oil. The oil was partially dissolved in
- 25 methanol and the insoluble materials present removed by filtration through diatomaceous earth. The resulting clear solution was treated with p-toluenesulfonic acid until neutral and the solvent removed in vacuo. The resulting residue was treated with ethanol and evaporated
- 30 in vacuo two times. The residue was then dissolved in 40 ml of hot ethanol and filtered through diatomaceous earth. The filtrate was treated with ether to the cloud point and the mixture allowed to crystallize at room temperature. The resulting crystals were filtered and
- 35 washed with ether to yield 10.6 g (39%) of crude product. One recrystallization from ethanol/ether afforded pure

N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamine 4-methylbenzenesulfonate, a white solid, mp 105-106.5°C.

5 Example 11

Using the procedure of Example 10 and substituting equivalent quantities of the appropriate amide for N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamide there were obtained as products:

10 N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxybenzeneethanamine (E)-2-butenedioate (1:1), mp 126-131°C;

15 N-(2-Phenylethyl)-2-iodo-5-methoxybenzeneethanamine perchlorate, mp 178-179°C;

 N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodo-N-methyl-5-methylthiobenzenepropanamine oxalate, mp 132-135°C;

20 N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-fluoro-2-iodo-N-methylbenzenepropanamine oxalate, mp 129-131°C.

Example 12

4-(3-Methoxyphenyl)-3-buten-2-one

25 A solution of 19.08 ml of 10% sodium hydroxide solution was added dropwise to a mixture of 103.6 g (0.761 mole) of 3-methoxybenzaldehyde, 117.2 g (2.02 mole) of acetone and 75 ml of water. The temperature was kept between 24 and 28° by intermittent application of cooling. After 2.75 hours the mixture was acidified with dilute hydrochloric acid and partitioned between CH₂Cl₂ and water. The organic layer was washed with water, dried with MgSO₄ and concentrated in vacuo to give 132.6 g of a yellow oil.

30 The oil was distilled in a Kugelrohr at 0.5 Torr. A forerun, bp 90-110°C, was taken and discarded. The main fraction was taken between 110 and 120°C. There was

35

-26-

obtained 91.68 g (68% yield) of 4-(3-methoxyphenyl)-3-buten-2-one as a yellowish oil.

Example 13

5

1-(3-methoxyphenyl)-1-octen-3-one

Following the procedure of Example 12 and substituting an equivalent quantity of 2-heptanone for acetone there was
10 obtained 1-(3-methoxyphenyl)-1-octen-3-one, bp 110-134°C, 0.3 mm/hg.

Example 14 .

15 4-(3-Methoxyphenyl)-2-butanone

A solution of 30.1 g of 4-(3-methoxyphenyl)-3-buten-2-one in 200 ml of MeOH was hydrogenated over 200 mg of 10% palladium on carbon for two hours. The catalyst was
20 filtered and the solvent evaporated in vacuo to give 30.2 g of yellow oily 4-(3-methoxyphenyl)-2-butanone.

Example 15

25 1-(3-methoxyphenyl)octan-3-one

Following the procedure of Example 14 and substituting an equivalent quantity of 1-(3-methoxyphenyl)-1-octan-3-one for 4-(3-methoxyphenyl)-3-buten-2-one there was obtained
30 as the product 1-(3-methoxyphenyl)octan-3-one as a colorless oil.

Example 16Ethyl 3-(2-bromophenyl)-2-methyloxiraneacetate

- 5 A 50 g (0.27 mole) sample of 2-bromobenzaldehyde was added
to 33.3 g of dry potassium t-butoxide under N_2 at -78° . A
48.9 g (0.27 mole) sample of ethyl 2-bromopropionate was
added slowly with stirring. The mixture was allowed to
warm to room temperature and stir for 18 hr. The mixture
10 was partitioned between ether and dilute HCl. The ether
was washed with brine, dried ($MgSO_4$) and the solvent
evaporated in vacuo. The residue was distilled under
vacuum to give 53.2 g (69% yield) of ethyl 3-(2-
bromophenyl)-2-methyloxiraneacetate as an oil, bp 110-
15 120°C, 0.005 mm/Hg.

Example 172-Bromophenyl-2-propanone

- 20 A solution of 69.3 g (0.243 mole) of ethyl 3-(2-bromo-
phenyl)-2-methyl oxiraneacetate in 100 ml of 95% ethanol
was added to 9.72 g (0.243 moles) of sodium hydroxide.
The solution was heated under reflux for 3 hr. The sol-
25 vent was evaporated in vacuo. The residue was partitioned
between ether and dilute HCl. The ether was washed with
brine, dried ($MgSO_4$) and the solvent evaporated in vacuo
to give 62.9 g of a yellow oil. The oil was heated at
240° in a kugelrohr to give 38.4 g of distillate. The
30 material was distilled through a Vigreux column to give
24.7 g (47% yield) of yellow oily 2-bromophenyl-2-
propanone, mp 60-65° (0.005 mm Hg).

Example 18

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxyalpha-methybenzene ethanamine hydrochloride.

- 5 A mixture of 20.0 g (0.06 mole) of (2-iodo-5-methoxyphenyl)-2-propanone and 11.9 ml (0.07 mole) of 3,4-dimethoxyphenylethylamine in 200 ml of chloroform was stirred overnight over 240 g of 5A molecular sieves. The
- 10 solvent was evaporated in vacuo to give 26.39 g of the corresponding imine. The imine was dissolved in 200 ml of methanol and 4 ml of methanolic hydrogen chloride and 2.91 g (0.046 mole) of sodium cyanoborohydride were added. The mixture was stirred for 3 days under an
- 15 atmosphere of N₂. Additional methanolic hydrogen chloride was added over a several hour period to pH 1. The mixture was allowed to stand at room temperature overnight and the solvent evaporated in vacuo. The residue was partitioned between ether and aqueous sodium hydroxide. The ether
- 20 layer was washed with water and brine, dried (K₂CO₃) and evaporated in vacuo. The residue (24.5 g of an oil) was treated with ethereal hydrogen chloride to give the hydrochloride salt. It was recrystallized successively from 2-propanol and ethanol to afford N-[2-(3,4-
- 25 dimethoxyphenyl)ethyl]-2-iodo-5-methoxyalphamethyl benzenethanamine hydrochloride, mp 170-172°C.

Example 19

- 30 Following the procedure of Example 18 and substituting 3,4-dichlorophenethylamine for 3,4-dimethoxyphenethylamine there was obtained as the product N-[2-(3,4-dichlorophenyl)ethyl]-2-iodo-5-methoxyalphamethylbenzenethanamine (E)-2-butenedioate (1:1), mp 91-93°C.

Example 202-Iodo-5-methoxy-N,alphadimethylbenzenepropanamine
Hydrochloride.

5

A solution of 19.41 g (0.625 mole) of methylamine in 400 ml of anhydrous methanol was treated with 37.92 g (0.125 mole) of 4-(2-iodo-5-methoxyphenyl)-2-butanone, 6.28 g (0.1 mole) of sodium cyanoborohydride and 21.07 g (0.312 mole) of methylamine hydrochloride and allowed to stir at room temperature under an atmosphere of nitrogen for 2-1/2 hours. The resulting mixture was cooled in an ice bath and treated with concentrated hydrochloric acid to pH 1. The solvent was evaporated in vacuo and the residue partitioned between 1.5 l of water and 600 ml of ether. The water layer was separated and treated with 50% sodium hydroxide solution until basic. The resulting crude product was extracted into 500 ml of ether, washed with brine, and the brine layer extracted with an additional 400 ml portion of ether. The combined ether layers were dried over anhydrous potassium carbonate and evaporated in vacuo to yield 31.09 g (78%) of crude oil. The oil was dissolved in methanol and treated with ethereal hydrogen chloride until neutral. Ether was added to the mixture and the resulting hydrochloride salt separated by filtration to give 19.75 g (44%) of crude product. One recrystallization from 2-propanol yielded pure 2-iodo-5-methy-N-alphadimethylbenzenepropanamine hydrochloride a white solid, mp 189-190°C.

Example 212-Iodo-5-methoxy-N,alphadimethyl-N-[(phenyl)butyl]benzene-ethanamine.

5

A solution of 3.5 g (12.1 mmole) of (2-iodo-5-methoxy-phenyl)-2-propanone, 2.05 ml (12.7 mole) 4-phenylbutyl-amine and 23 mg (.13 mmole) toluenesulfonic acid in 35 ml of toluene was heated under reflux for 45 minutes. The solvent was evaporated in vacuo. The residue was taken up in 18 ml MeOH and 0.85 g (1.6 mmole) of sodium cyanoborohydride and 0.13 ml of saturated ethereal hydrogen chloride were added. The mixture was stirred for 16 hours. To the mixture was added 2.45 ml (30.2 mmoles) of formalin and 3.69 g (44.8 mmole) sodium cyanoborohydride. The mixture was stirred 5 hours. It was acidified to pH 1 by the addition of concentrated HCl. The MeOH was evaporated in vacuo and the solution made basic with NaOH and extracted with CH₂Cl₂. The organic layer was washed with water, dried (K₂CO₃) and evaporated in vacuo to give 4.15 g of an oil. The oxalate salt was prepared from MeOH and recrystallized from 2-propanol/methanol to give 1.96 g (30% yield) of white crystalline 2-iodo-5-methoxy-N,alphadimethyl-N-[(phenyl)butyl]benzene-ethanamine oxalate, mp 133-135°C.

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20

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Example 22N-[3-(2-Iodo-5-methoxyphenyl)-1-methylpropyl]-3,4-dimethoxy-N-methylbenzeneacetamide

30

35

A solution of 17.87 g (0.056 mole) of 2-iodo-5-methoxy-N,alphadimethylbenzenepropanamine in 58 ml of dry methylene chloride was added dropwise to a cooled (5°C) solution of 3,4-dimethoxyphenylacetyl chloride in 68 ml of dry methylene chloride over a period of five minutes while

stirring under an atmosphere of nitrogen. After about two minutes of stirring, 5.67 g (0.056 mole) of triethylamine was added followed by an additional 20 ml of dry methylene chloride. The reaction mixture was allowed to warm to room temperature while stirring overnight. An additional 80 ml of methylene chloride was added and the mixture washed successively with 200 ml of water, 300 ml of 5% hydrochloric acid, and 200 ml of sodium hydroxide solution. The organic phase was dried over anhydrous magnesium sulfate and evaporated in vacuo to yield 27.5 g (99%) of N-[3-(2-iodo-5-methoxyphenyl)-1-methylpropyl]-3,4-dimethoxy-N-methylbenzeneacetamine as an orange gum, MS (high resolution):

Calculated for M^{+1} : 497.1063.
Found: 497.1057.

Example 23

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N,alphadimethylbenzenepropanamine.

A solution of 27.19 g (0.055 mole) of N-[3-(2-iodo-5-methoxyphenyl)-1-methylpropyl]-3,4-dimethoxy-N-methylbenzeneacetamide was added dropwise over a 30 minute period with stirring to 165 ml of 1M $BH_3 \cdot THF$ under an atmosphere of nitrogen. The mixture was heated to reflux for 2.5 hours and then cooled to 0°C in an ice bath. A mixture of 50 ml THF and 25 ml of water was added carefully and the resulting mixture was evaporated in vacuo to remove the THF. The residue was treated with 100 ml of water and 5.79 g of sodium hydroxide and heated to reflux for four hours. Heating was interrupted and an additional 10 g of sodium hydroxide was added. Heating was resumed for another hour. The mixture was cooled and extracted with two 300 ml portions of ether. The combined

ether extracts were washed with water, brine, and dried over anhydrous potassium carbonate. The solvent was removed in vacuo to give 27.66 g of a yellow oil. The oil was partitioned between ether and 400 ml of 10% hydrochloric acid, at which time the resulting oil was separated, dissolved in a large volume of water, and washed with ether. The aqueous phase was treated with 10% sodium hydroxide solution until basic and extracted several times with ether. The combined ether layers were dried over anhydrous potassium carbonate and evaporated in vacuo to yield 20.98 g (79%) of a yellow oil.

The oil was converted to a crystalline oxalate salt from methanol, mp 189-190°C. The oxalate salt was partitioned between methylene chloride and water and treated with a slight excess of sodium hydroxide. The methylene chloride layer was separated, dried over anhydrous potassium carbonate, and evaporated in vacuo to yield 16.33 g of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N,alphadimethylbenzenepropanamine as a colorless oil.

Example 24

1-Methoxy-3-(2-nitro-1-propenyl)benzene

A mixture of 71.9 g (0.528 mole) of m-anisaldehyde, 118.9 g (1.584 mole) of nitroethane, 40.7 g (0.528 mole) of ammonium acetate, and 350 ml of glacial acetic acid was heated to reflux for one hour. The mixture was then allowed to cool and partitioned between ether and water. The ether layer was separated and washed sequentially with water, 3N sodium hydroxide, water and brine. The organic phase was dried over anhydrous magnesium sulfate and evaporated in vacuo to give the crude product. After a preliminary distillation at 125°C/0.0001 mm, the product was finally crystallized from absolute ethanol to yield the pure product, a yellow solid, mp 40-42°C.

Example 253-Methoxy- α -methylbenzeneethaneamine

- 5 Two separate 3 liter three-necked round bottom flasks were each equipped with an overhead stirrer, condenser, addition funnel and nitrogen inlet tube. The flasks were purged with nitrogen and charged with 19.64 g (0.517 mole) of lithium aluminum hydride and 600 ml of anhydrous ether.
- 10 To each flask was slowly added a solution of 25 g (0.129 mole) of 1-methoxy-3-(2-nitro-1-propenyl)benzene in 150 ml of anhydrous ether. An additional 500 ml of anhydrous ether was added to each flask, and the mixture allowed to stir overnight. After cooling in an ice bath,
- 15 each reaction was treated cautiously and sequentially with 20 ml of water, 20 ml of 3N sodium hydroxide, and 60 ml of water, while maintaining cooling and stirring in the ice bath. Cooling and stirring were continued for 30 minutes, after which time the batch was removed and stirring
- 20 continued until the inorganics formed a white solid. The inorganics were removed by filtration and washed with ether. The combined ether filtrates were washed with dilute sodium hydroxide, water, and brine. The ether layer was dried over anhydrous potassium carbonate and
- 25 filtered. The filtrate was treated with ethereal hydrogen chloride to form the hydrochloride salt (mp 115-118°C) of the product, which was then converted back to yield 20.4 g of the free base, an oil.

30 Example 26

1-(3,5-Dichlorophenyl)-3-methyl-1-butyne-3-ol

- 35 A mixture of 25.5 g (0.094 mole) of 3,5-dichloroiodobenzene, 550 ml dry triethylamine, 12 g (0.14 mole) of 2-methyl-2-hydroxy-3-butyne, 0.42 g (0.0019 mole)

palladium (II) acetate, and 1 g (0.0038 mole) of triphenylphosphine was heated to reflux under nitrogen for four hours. The resulting mixture was cooled, diluted with ether and washed with two 500-ml portions of 3N hydrochloric acid. The ether layer was separated, dried over anhydrous magnesium sulfate, and evaporated in vacuo to yield the crude product as an oily residue. The purified product was obtained by distillation to yield 7.95 g, bp 115-125°C/0.0001 mm.

10

Example 27

1,3-Dichloro-5-ethynylbenzene

15 A mixture of 7.95 g (0.0655 mole) of 1-(3,5-dichlorophenyl)-3-methyl-1-butyn-3-ol and 30 g of sodium hydroxide in 150 ml of dry toluene was heated to reflux with stirring for 3.5 hours. The toluene was removed in vacuo to yield a brown solid residue. The residue was triturated with hexane and the resulting hexane solution washed with aqueous sodium thiosulfate solution. The hexane layer was separated and evaporated in vacuo to yield the crude product. Recrystallization from hexane yielded 4.15 g of pure product, mp 80-81.5°C.

25

Example 28

Copper I (3,5-Dichlorophenyl)acetylide

30 A mixture of 77 g of copper (II) sulfate pentahydrate and 30 ml of concentrated ammonium hydroxide was stirred under an atmosphere of nitrogen and 125 ml of water added. Stirring was continued until all of the copper sulfate dissolved, then 43 g of hydroxylamine hydrochloride was added with continued stirring for 30 minutes to form a pale blue solution. A solution of 4.15 g of 1,3-dichloro-5-ethynylbenzene in 150 ml of absolute ethanol was added

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dropwise with stirring to the pale blue copper solution. Stirring was continued an additional two hours, the mixture filtered and the resulting bright yellow product, a solid, washed sequentially with water, ethanol, and ether. The product was dried in vacuo to yield 4.25 g of copper (I) (3,5-dichlorophenyl)acetylide.

Example 29

Using the procedures of Examples 26 and 27 substituting the appropriate Ar-iodide for 3,5-dichloriodobenzene the following Ar-acetylenes were prepared respectively:

Ar-iodide	Ar-acetylene	% Yield	bp 20 mm/Hg
3-Iodotoluene	3-Methylphenylacetylene	88	90-110°
4-Iodoanisole	4-Methoxyphenylacetylene	45	90°
2-Iodothiophene	2-Ethynylthiophene	54	90-110°

Example 30

Using the procedure of Example 28 and employing equivalent quantities of the appropriate Ar-acetylene in place of 1,3-dichloro-5-ethynylbenzene the following copper (I) Ar-acetylides were obtained as bright yellow amorphous powders respectively:

<u>Ar-acetylene</u>	<u>Cu (I) Ar-acetylide</u>	<u>% Yield</u>
3-Methylphenyl-acetylene	Cu (I) 3-Methylphenyl-acetylide	32

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4-Methoxyphenyl- acetylene	Cu (I) 4-methoxyphenyl- acetylide	70
2-Ethynylthiophene	Cu (I) 2-thienylacetylide	9
4-Chlorophenyl- acetylene	Cu (I) 4-Chlorophenyl- acetylide	88

Example 31

N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N-methyl-2
(phenylethynyl)benzenepropanamine Hydrochloride Hydrate
(8:8:1).

A 100 ml round bottom flask was charged with a solution of 2.09 ml (19.0 mmole) of 98% phenylacetylene in 15 ml of dry THF. The solution was cooled to 0°C and 11.62 ml (19.6 mmole) of n-butyllithium (1.6 N in hexane) was added (solution turns from yellow to dark green). The mixture was allowed to stir for 15 minutes at 0°C and transferred via cannula under argon to a flask containing 2.53 g (18.6 mmole) of anhydrous zinc chloride while maintaining a temperature of 0°C. The mixture was stirred for 15 minutes.

A solution of 7.27 g (15.5 mmole) of N-[2-(3,4-dimethoxyphenyl) ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamine and 0.36 g (0.31 mmole) of tetrakis(triphenylphosphine) palladium in 100 ml THF was added to the reaction flask via cannula. The mixture was allowed to warm to room temperature and stir for 3 1/2 hours. The reaction was quenched by addition of 20 ml of water and then partitioned between 500 ml of methylene chloride and 500 ml water. The organic phase was separated, washed with 500 ml of 5% hydrochloric acid, 500 ml of 5% sodium hydroxide, dried over anhydrous potassium carbonate, and

evaporated in vacuo to yield an orange oil. The oil was dissolved in methanol and cooled in ice to form a yellow solid. The solid was removed by filtration and the filtrate evaporated in vacuo. The resulting residue was dissolved in ether and filtered through diatomaceous earth to remove some slight turbidity. The filtrate was evaporated in vacuo to yield an orange oil which was dissolved in methanol and treated with ethereal hydrogen chloride to pH 7.0 to 7.6. The solvent was removed in vacuo and the residue crystallized from t-butanol/ether with cooling. One recrystallization from t-butanol/ether afforded pure N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methoxy-N-methyl-2-(phenylethynyl)benzenepropanamine hydrochloride hydrate (8:8:1), a white solid, mp 122-123.5°C.

Anal Calc'd for $C_{29}H_{33}NO_3 \cdot HCl \frac{1}{8} H_2O$:

C, 72.22; H, 7.16; N, 2.90; H_2O , 0.47

Found: C, 71.84; H, 7.10; N, 2.89; H_2O , 0.29

Example 32

N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N, alpha-dimethyl-2-[(phenyl)ethynyl] benzenepropanamine Hydrochloride.

A solution of 4.55 ml (41.4 mmole) of phenylacetylene in 40 ml of dry THF was cooled to 0° and 21.4 ml of 1.9 M butyllithium in hexane (41.4 mmole) was added. The resulting solution was stirred for 15 minutes under N_2 then transferred to a flask containing 5.53 g (40.6 mmole) of dry $ZnCl_2$. The mixture was stirred 15 minutes at 0° and a solution of 16.33 g (33.8 mmole) of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N, alpha-dimethylbenzenepropanamine and 0.78 g (0.68 mmoles) of tetrakis-(triphenylphosphine) palladium (0) in 100 ml of THF was added. The mixture was allowed to warm to room

temperature and stirred for 24 hours. The mixture was diluted with CH_2Cl_2 and washed with water, 5% HCl, dilute NaOH, dried (K_2CO_3) and the solvent evaporated in vacuo. The residue was dissolved in MeOH and ethereal hydrogen chloride added. The solvent was evaporated in vacuo and the residue crystallized from 2-propanol/ether. The solid was recrystallized from 2-propanol/ether to give 5.53 g (33% yield) of N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methoxy-N,alphadimethyl-2-(phenyl)ethynyl benzenepropanamine hydrochloride, mp 119-122°C.

Anal. Calcd. for $\text{C}_{30}\text{H}_{35}\text{NO} \cdot \text{HCl} \cdot 0.5 \text{ H}_2\text{O}$

C, 71.62; H, 7.41; N, 2.78; H_2O , 1.79.

Found: C, 71.65; H, 7.43; N, 2.70; H_2O , 1.45.

Example 33

Using the procedure of example 32 and employing equivalent quantities of the appropriate iodoamine in place of N-[2-(3,4-dimethoxyphenyl)ethyl]2-iodo-5-methoxy-N-methyl-benzenepropanamine, the following products were obtained respectively.

	<u>Product</u>	<u>mp</u>
25	N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-2-(phenylethynyl)benzeneethanamine Hydrochloride	160-163
30	5-Methoxy-N-(2-phenylethyl)-2-(phenylethynyl)-benzenepropanamine (E)-2-Butenedioate (2:1)	150-151
	N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-2-(phenylethynyl)benzenepropanamine (E)-2-Butenedioate	151-153

- N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-
alpha-methyl-2-(phenylethynyl)benzeneethanamine
(E)-2-Butenedioate Hydrate (6:3:2) 165-167
- 5 N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N-
methyl- α -pentyl-2-phenylethynyl)benzenepro-
panamine Oxalate (1:1) 131-133
- 10 N-[2-(3,4-Dichlorophenyl)ethyl]-5-methoxyalpha
methyl-2-[(phenyl)ethynyl]benzeneethanamine (E)-
2-Butenedioate 171-173
- 15 N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-fluoro-N-
methyl-2-[(phenyl)ethynyl]benzenepropanamine
Oxalate 145-147
- 20 N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-5-
methylthio-2-[(phenyl)ethynyl]benzenepropanamine
Oxalate 156-158

Example 34

- 25 N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-2-[(4-methoxy-
phenyl) ethynyl]-N-methylbenzenepropanamine Ethanedioate
(1:1).

30 A mixture of 3 g (6.4 mmole) of N-[2-(3,4-dimethoxy-
phenyl)ethyl]-2-iodo-5-methoxy-N-methylbenzenepropanamine,
1.5 g (7.7 mmole) of Copper (I) (4-methoxyphenyl)-
acetylide, and 75 ml of pyridine was heated overnight to
reflux under an atmosphere of nitrogen. An additional
0.8 g of the copper compound was added and refluxing con-
tinued another four hours. The solvent was removed in
35 vacuo and the residue partitioned between ether and con-
centrated ammonium hydroxide. The resulting solid was
removed by filtration and the aqueous phase extracted with

additional ether. The combined ether extracts were extracted with two portions of 3N hydrochloric acid. The acid extract was basified by addition of solid sodium hydroxide and extracted with ether. The ether layer was washed with water, brine and dried over anhydrous potassium carbonate. The ether was removed in vacuo and the residue partially purified by flash chromatography on silica using a 2:1 mixture of ethyl acetate:cyclohexane followed by HPLC purification on silica using a 9:1 mixture of ethyl acetate:cyclohexane. The oxalate salt was prepared by addition of one equivalent of oxalic acid in a mixture of 2-propanol and methanol. One recrystallization from 2-propanol afforded N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methoxy-2-[(4-methoxyphenyl)ethynyl]-N-methylbenzenepropanamine ethanedioate (1:1), a white solid, mp 148-150°C.

Example 35

20 2-[(4-Chlorophenyl)ethynyl]-N-[2-(3,4-dimethoxyphenyl)-ethyl]-5-methoxy-N-methylbenzenepropanamine (E)-2-Butenedioate.

Using the procedure of the foregoing example and substituting an equivalent quantity of Copper (I) (4-chlorophenyl)acetylide for copper (I) (4-methoxyphenyl)acetylide there was obtained as a white crystalline product 2-[(4-chlorophenyl)ethynyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methoxy-N-methylbenzene propanamine (E)-2-butenedioate, mp 164-166°C.

Example 36

5-Methoxy-N,alphadimethyl-N-[(phenyl)butyl]-2-[(phenyl)ethynyl]benzeneethanamine hydrochloride.

5

The free base of 2-iodo-5-methoxy-N,alphadimethyl-N-[(phenyl)butyl]benzeneethanamine hydrochloride (1.66 g, 3.1mmole) was dissolved in 10 ml of triethylamine and 0.68 ml (6.2 mmole) of phenylacetylene, 11 mg (0.015 mmole) of bis(triphenylphosphine) palladium (II) chloride and 6 mg (.03 mmole) copper (I) iodide were added. The mixture was stirred under argon at room temperature for 20 hours. An additional 6 mg copper (I) iodide and 11 mg bis(triphenylphosphine) palladium (II) chloride were added. The mixture was stirred for 20 hours. The solvent was evaporated in vacuo. The residue was taken up in CH_2Cl_2 . The CH_2Cl_2 was washed with dilute HCl and dilute NaOH solution, dried (K_2CO_3) and the solvent evaporated in vacuo. A hydrochloride salt was prepared from ethereal hydrogen chloride and recrystallized twice from 2-propanoether to give 0.46 g of 5-methoxy-N,alphadimethyl-N-[(phenyl)butyl]-2-[(phenyl)ethynyl]benzeneethanamine hydrochloride, mp 133-135°C.

25 Example 37

2-[(Phenyl)ethynyl]phenyl-2-propanone.

A solution of 28.3 g (112 mmole) of 2-bromophenyl-2-propanone, 14.7 ml (134 mmole) of phenylacetylene, 1.8 g (2.24 mmole) of bis(triphenylphosphine) palladium (II) chloride and 0.85 g (4.48 mmole) of copper (I) iodide in 250 ml of triethylamine under nitrogen was heated under reflux for 3 1/2 hours. An additional 3.6 ml of phenylacetylene, 0.36 g of palladium complex and 0.1 g copper (I) iodide were added. The mixture was heated under

reflux for 3 1/2 hours. An additional 5.0 ml of phenyl-
acetylene, 0.36 g of palladium complex and 0.17 g of
copper (I) iodide were added. The mixture was heated
under reflux for 2 hours. An additional 5.0 ml of phenyl-
5 acetylene was added. The mixture was heated under reflux
for 3 1/2 hours. The solvent was evaporated in vacuo and
the residue taken up in ether. The ether was washed with
water and brine, dried (K_2CO_3) and the solvent evaporated
in vacuo. The residue was flash chromatographed on silica
10 gel with ethyl acetate:hexane, 9:1, as eluant. The
solvent was evaporated from the major compound bearing
fraction to afford 21.2 g (81% yeild) of 2-[(phenyl)-
ethynyl]phenyl-2-propanone as an oil.

15 Example 38

[2-(5-Methoxyphenyl)ethynyl] phenyl-2-propanone.

A solution of 5.5 g (18.9 mmole) 2-iodo-5-methoxyphenyl-2-
20 propanane (18.9 mmole), 4.15 ml (37.8 mmole) of
phenylacetylene, 0.037 g cuprous iodide (1 mole percent)
and 0.066 g of bis (triphenylphosphine) palladium (II)
chloride (5 mole percent) in 60 ml of triethylamine was
stirred for 18 hours under N_2 at room temperature. The
25 mixture was partitioned between water and ether. The
ether layer was washed succesively with cold hydrochloric
acid solution, water and brine. It was dried over $MgSO_4$
and the solvent evaporated in vacuo to give 5.6 g (100%
yield) of brown crystals. Recrystallization from
30 methylcyclohexane afforded pure [2-(5-methoxyphenyl)-
ethynyl]phenyl-2-propanone, mp 60 - 62°C.

Example 39

N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N-methyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate

5

A solution of 1.7 g (4.09 mmole) of N-[2-(3,4-dimethoxy-phenyl)ethyl]-5-methoxy-2-(phenylethynyl)benzeneethanamine in 30 ml of methanol was treated with 0.85 ml (10.2 mmole) of 37% aqueous formaldehyde solution and 0.95 g
10 (15.1 mmole) of sodium cyanoborohydride. The mixture was stirred under an atmosphere of nitrogen for six hours, methanolic hydrogen chloride was added to pH 1, and the mixture stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue partitioned
15 between 3 N sodium hydroxide and ether. The organic phase was separated, washed with brine, dried over anhydrous potassium carbonate and evaporated in vacuo to yield crude free base of the product. The free base was combined with one equivalent of fumaric acid in 2-propanol and allowed
20 to crystallize overnight with cooling. Filtering afforded 1.73 g of nearly pure product which was recrystallized from a mixture of 95% ethanol and 2-propanol to yield pure N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methoxy-N-methyl-2-(phenylethynyl)benzeneethanamine (E)-2-butenedioate
25 (1:1), mp 152.5-154°C.

Anal. Calc'd. for: $C_{28}H_{31}NO_3 \cdot C_4H_4O_4$:

C, 70.44; H, 6.47; N, 2.57

Found: C, 70.41; H, 6.48; N, 2.54

30

Example 40

By employing the appropriate starting materials and following the procedure of the foregoing example the
35 following were prepared:

N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate (1:1), mp 124-126°C

- 5 N-[2-(3,4-Dichlorophenyl)ethyl]-5-methoxy-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate (1:1), mp 124-127°C

Example 41

10

5-Methoxy-N-methyl-N-(2-phenylethyl)-2-(phenylethynyl)-benzenepropanamine hydrochloride

- A mixture of 5.54 g (0.015 Mol) of 5-methoxy-N-(2-phenylethyl)-2-(phenylethynyl)benzenepropanamine, 1.34 g (0.0165 Mol) of 37% aqueous formaldehyde solution, and 2.16 g (0.045 mole) of 95 - 97% formic acid was heated on a steam bath for three hours until gas evolution ceased. The volatiles were removed in vacuo and the residue dissolved in water. Aqueous sodium hydroxide (1%) was added and the mixture extracted with two portions of ether. The combined ether extracts were washed with water and brine, dried over anhydrous potassium carbonate, and evaporated in vacuo to yield 4.92 g of yellow oil. The oil was dissolved in a minimum volume of methanol and neutralized with ethereal hydrogen chloride. Evaporation of the resulting solution yielded a yellow oil which crystallized from a mixture of t-butanol and ether to form white crystals. One recrystallization from t-butanol ether gave pure 5-methoxy-N-methyl-N-(2-phenylethyl)-2-(phenylethynyl)benzenepropanamine hydrochloride, a white solid, mp 111-112°C.

- Anal. Calc'd. for $C_{27}H_{29}NO \cdot HCl$:
35 C, 77.21; H, 7.20; N, 3.34
Found: C, 77.23; H, 7.21; N, 3.35

Example 42

5 N-[2-(3,4-Dimethoxyphenyl)-1-methylethyl]-5-methoxy-alpha-
methyl-2-phenylethynyl)benzeneethanamine (E)-2-Butene-
dioate (20:17)

10 A mixture 5.0 g (18.8 mmole) of 5-methoxy-2-methyl-2-
(phenylethynyl)benzeneethanamine, 3.3 ml (18.8 mmole) of
3,4-dimethoxyphenylacetone and 20 g of 5A molecular sieves
15 in 45 ml of CHCl_3 was stirred at room temperature for 6
hours. An additional 0.3 ml of 3,4-dimethoxyphenylacetone
and 20 g of molecular sieves were added and the mixture
allowed to stand overnight. A third 20 g portion of
molecular sieves was added and stirring resumed for 6
15 hours. The solids were removed by filtration and the
filtrate evaporated in vacuo to give a yellow oil consist-
ing of the corresponding imine.

20 The oil was dissolved in 50 ml of methanol and 0.72 g
(11.4 mmole) of sodium cyanoborohydride and 1 ml of
methanolic hydrogen chloride was added. The mixture was
stirred at room temperature overnight. The pH was
adjusted to pH 1 by the addition of methanolic hydrogen
chloride and stirring was continued for 2 hours. The
25 solvent was evaporated in vacuo and the residue was
partitioned between ether and 3 N sodium hydroxide solution.
The organic phase was washed with water and brine and
dried (K_2CO_3). The solvent was evaporated in vacuo to
give an oil which was treated with one equivalent of
30 fumaric acid in 2-propanol to give a crystalline salt
which was recrystallized from 95% ethanol to give 1.54 g
of N-[2-(3,4-dimethoxyphenyl)-1-methyl]-5-methoxy-
alphamethyl-2-(phenylethynyl)benzeneethanamine (E)-2-
butenedioate (20:17) as a white solid, mp 196-199°C.

Anal. Calc'd. for $C_{29}H_{33}NO_3 \cdot 0.85 C_4H_4O_4$:

C, 71.77; H, 6.77; N, 2.58.

Found: C, 71.69; H, 6.86; N, 2.68.

5 Example 43

N-[2-(3,4-Dimethoxyphenyl)ethyl]-alpha, N-dimethyl-2-(phenylethynyl)benzeneethanamine

10 A mixture of 2.4 g (10.2 mmole) of 2-[(phenyl)ethynyl]-phenyl-2-propanone, 1.73 g (10.2 mmole) of homoveratryl-amine and 35 g of 5A molecular sieves in 35 ml of chloro-
form was stirred overnight at room temperature under an
atmosphere of nitrogen. The mixture was filtered and the
15 sieves washed with chloroform. The filtrate was evaporated to yield 4.1 g (100%) of the corresponding imine.

The imine was dissolved in 40 ml of methanol and treated with 0.52 g (8.25 mmole) of sodium cyanoborohydride and
20 allowed to stir overnight under an atmosphere of nitrogen. An additional 0.2 ml of homoveratryl amine and 2 ml of methanolic hydrogen chloride was added and stirring continued another 24 hours. A third portion of homoveratryl amine (0.4 ml) and 2 ml of methanolic hydrogen chloride
25 was added and stirring resumed for another 24 hours. A 2.2 ml sample of 34% formaldehyde and 2.4 g of sodium cyanoborohydride were added. The mixture was stirred for three days, methanolic hydrogen chloride added to pH 1, and the mixture stirred for 30 minutes. The solvent was
30 removed in vacuo and the residue dissolved in chloroform, washed with 12% sodium hydroxide solution, dried over anhydrous potassium carbonate and evaporated in vacuo to yield 4.3 g a dark oil. The crude product was partially purified by flash chromatography in silica gel by elution
35 with acetone:methylene chloride. The fractions containing the desired product were evaporated in vacuo to yield

2.8 g of oily product. Further purification was accomplished by conversion to an oxalate salt in ethanol and regeneration of the free base to yield pure N-[2-(3,4-dimethoxyphenyl)ethyl]-alpha, N-dimethyl-2-(phenylethynyl)benzeneethanamine, an oil.

Anal. Calc'd. for $C_{28}H_{31}NO_2 \cdot 1/4H_2O$:

C, 80.44; H, 7.59; N, 3.35

Found: C, 80.55; H, 7.65; N, 3.29

Example 44

N-[(3,4-Dimethoxyphenyl)methyl]-5-methoxy-N,alpha-dimethyl-2-(phenylethynyl)benzeneethanamine hydrochloride

To a solution of 3.12 g (11.8 mmole) of [2-(5-methoxyphenyl)ethynyl]phenyl-2-propanone and 1.96 ml (13.0 mmole) of 3,4-dimethoxybenzylamine in 40 ml of CH_2Cl_2 was added 22 g of 5A molecular sieves. The reaction was stirred for two days. The sieves were removed by filtration and the solvent was evaporated in vacuo. The residue was dissolved in 15 ml of MeOH and 0.75 g (9.4 mmole) sodium cyanoborohydride and 1 ml of saturated ethereal hydrogen chloride were added. The mixture was stirred for 3 days. A 22 ml (29.5 mmole) sample of formalin, 3.5 g (43.7 mmole) of sodium cyanoborohydride and 10 ml of MeOH were added. The mixture was stirred for 16 hours. The mixture was acidified to pH 1 by the addition of concentrated HCl and stirred until bubbling ceased. The reaction was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was washed with dilute NaOH solution and water, dried (K_2CO_3) and the solvent evaporated in vacuo to give 4.9 g of an oily residue.

An oxalate salt was prepared from 1.27 g oxalic acid in MeOH. The MeOH was evaporated in vacuo and the salt crystallized from 2-propanol/ether. There was obtained 2.5 g (28% yield of crystalline N-[(3,4-dimethoxyphenyl)-methyl]-5-methoxy-N,alphadimethyl-2-[(phenyl)ethynyl]benzeneethanamine oxalate, mp 164-166°C. The oxalate was converted to the free base by partitioning between CH₂Cl₂ and NaOH. The CH₂Cl₂ was evaporated in vacuo and the hydrochloride prepared from 2-propanol/ether. There was obtained 1.5 g of the hydrochloride salt, mp 181-183.5°C.

Example 45

Ethyl 3-aminobenzenepropanoate hydrochloride

A suspension of 100 g (0.52 moles) of 3-nitrocinnamic acid in 800 ml glacial acetic acid and 100 ml of methanol was hydrogenated at 50 pounds per square inch over 2.5 g 10% palladium on carbon until four equivalents of hydrogen were absorbed. The catalyst was filtered off, the filtrates combined and the solvent was concentrated in vacuo leaving a brown glass of 3-aminobenzenepropanoic acid. To this was added 1 liter of ethanolic hydrogen chloride which was heated to reflux for five hours. The solvent was evaporated in vacuo leaving a purple solid. Recrystallization from ethyl acetate yielded 88.0 g (74%) of ethyl 3-aminobenzenepropanoate hydrochloride, mp 132-135°C.

Example 46

Ethyl 5-amino-2-iodobenzenepropanoate hydrochloride

To a solution of 88.0 g (0.38 moles) ethyl 3-amino-benzenepropanoate in 380 ml glacial acetic acid was added 97.3 g (0.38 moles) iodine and 96.0 g (0.57 moles) silver

acetate portionwise, alternating the additions beginning with the iodine. After two hours of stirring 10 g of iodine was added and stirring was continued for an additional hour. The reaction mixture was filtered and the solid washed well with acetic acid. The filtrate was extracted with chloroform. The chloroform layer was washed with sodium bisulfite solution then evaporated in vacuo. The resulting red oil was converted to the hydrochloric acid salt giving 118.3 g (72%) of ethyl 5-amino-2-iodobenzenepropanoate hydrochloride, mp 124-127°C.

Example 47

Sodium 2-iodo-5-methylthiobenzenepropanoate

A mixture of 30 g (0.089 moles) of ethyl 5-amino-2-iodobenzenepropanoate, 30 ml water, 20 g ice and 45 ml of hydrochloric acid was stirred for one hour. The solution was cooled to 0°C and 5.8 g (0.084 moles) of sodium nitrite in 15 ml of water were added dropwise keeping the temperature below 5°C. After stirring for one hour the reaction mixture was added to a solution of 13.5 g (0.084 moles) of potassium ethyl xanthate in 20 ml of water. This was stirred for three hours. The reaction mixture was extracted several times with diethyl ether which was evaporated in vacuo. The resulting brown oil was taken up in 95% ethanol and 18.9 g (0.336 moles) of potassium hydroxide was added. After refluxing overnight under nitrogen the reaction was cooled. Methyl iodide (10.5 ml; 0.168 moles) was added and the reaction was stirred three more hours. The ethanol was evaporated in vacuo. The residue was partitioned between 3N hydrochloric acid and diethyl ether. The ether was washed with water, brine solution and dried over Mg SO₄. The ether was evaporated. Conversion to the sodium salt gave

14.3 g (49%) of sodium 2-iodo-5-methylthiobenzene-propanoate, mp 118-122°C.

Example 48

5

3-(5-Fluoro-2-iodophenyl)propionic acid

A mixture of 30 g (0.084 mole) of ethyl 3-(5-amino-2-iodophenyl) propionate 45 ml of concentrated hydrochloric
10 acid, 25 ml of water, and 40 g of ice was stirred for 40 minutes then cooled to -10°C. A solution of 5.8 g of sodium nitrite in 20 ml of water was added dropwise with stirring while maintaining a temperature of -10°C. Stirring was continued for 1 1/2 hours then 13 ml of 65%
15 hexafluorophosphoric acid was added slowly and the mixture allowed to warm to room temperature and stirring for a period of one hour. The resulting solid as removed by filtration and wahed with water, 1:4::ethanol:water, and finally water. The solid was dried in vacuo, placed in
20 500 ml of xylene and heated at 130° for 2.5 hours, until gas evolution ceased. The solvent was removed in vacuo and the residue partially dissolved in ether. The insolubles were removed by filtration and the filtrate washed with sodium bicarbonate solution, 3 N hydrochloric
25 acid, water, and brine. The solvent was removed in vacuo to yield a brown oil which was purified by flash chromatography on silica using mixtures of ethyl acetate and hexane as the eluting solvent. The eluate was stripped in vacuo, the residue dissolved in ether,
30 insolubles removed by filtration, and finally the solvent removed in vacuo to yield 9.3 g of nearly pure fluoro-iodo ester, a yellow oil.

The ester was dissolved in 100 ml of methanol and treated
35 with 15.5 ml of 3 N sodium hydroxide solution. The mixture was refluxed for three hours and the solvent

removed in vacuo. The resulting residue was poured into 3N hydrochloric acid while cooling by addition of ice. The aqueous mixture was extracted with ether, the ether washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to yield 8.9 g of 3-(5-fluoro-2-iodophenyl)propionic acid, a yellow oil.

Example 49

10 N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N, α -dimethyl-2-[4-(trifluoromethyl)phenylethynyl]benzeneethanamine (E)-2-Butenedioate (2:1)

15 To a deoxygenated solution of 5.0g (10.6 mmole) of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N, α -diethyl benzeneethanamine in 50 ml of triethylamine under Ar was added 0.25g (0.21 mmole) of tetrakis(triphenylphosphine)-palladium (0), 0.08g (0.43 mmole) of CuI and 2.2g (12.8 mmole) of p-trifluoromethylphenylacetylene. The
20 reaction was heated under reflux for 16 hr. The mixture was cooled and filtered. Ether was added. The solvent was evaporated. The residue was taken up in MeOH and filtered. The solvent was evaporated. The residue was partitioned between water and ether. The ether layer was
25 washed with brine, dried (K_2CO_3) and the solvent evaporated in vacuo. A 1.0g sample of oxalic acid was added to the residue and the oxalate salt was recrystallized twice from 95% ethanol to give 2.8 of a solid. The oxalate salt was partitioned between CH_2Cl_2
30 and dilute NaOH solution. The organic solution was dried (K_2CO_3) and the solvent evaporated in vacuo. The residue was taken up in 2-propanol and 0.5g of fumaric acid was added. There was obtained, after collection of the precipitated salt by filtration, 1.97g of the title
35 compound as a white solid, mp 117.5-119.5°C.

Example 50

Using the procedure of Example 49 and substituting an equivalent quantity of the appropriately substituted phenylacetylene for p-trifluoromethylphenylacetylene, there were obtained as products respectively:

		<u>mp °C</u>
10	4-[[2-[2-[[2-(3,4-Dimethoxyphenyl)ethyl]methyl-amino]propyl]-4-methoxyphenyl]ethynyl]benzonitrile E-2-Butenedioate (2:1)	130-132
15	2-[[3,5-Bis(trifluoromethyl)phenyl]ethynyl]-N-[2-(3,4 dimethoxyphenyl)ethyl]-5-methoxy-N,α-di-methylbenzeneethanamine	yellow oil
20	N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N,α-dimethyl-2-[[4-(methylthio)phenyl]ethynyl]benzeneethanamine hydrochloride	93-95
25	N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N,α-dimethyl-2-[[4-(methylsulfinyl)phenyl]ethynyl]benzeneethanamine Hydrochloride (1:1)	199-201
	N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-[[4-fluorophenyl]ethynyl]-5-methoxy-N,α-dimethylbenzeneethanamine (E)-2-Butenedioate (1:1)	132.5-134
30	N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N,α-dimethyl-2-[[4-(dimethylamino)phenyl]ethynyl]benzenethanamine	99-100.5
35	N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methoxy-N,α-dimethyl-2-[[4-(1-methylethyl)phenyl]ethynyl]benzeneethanamine	55-6

Example 51

Using the procedure of Example 21 and employing the appropriate amine in place of 4-phenylbutylamine and the appropriate ketone, (2-iodo-5-methoxyphenyl)-2-propanone or 4-(2-iodo-5-methoxyphenyl)-2-butanone there were obtained as products respectively:

		<u>mp °C</u>
10	N-[2-(3,4-Dichlorophenyl)ethyl]-2-iodo 5-methoxy-N,α-dimethyl-benzeneepropanamine p-toluenesulfonate	160-162
15	2-Iodo-5-methoxy-N,α-dimethyl-N-[(3- phenyl)propyl]benzeneethanamine ethanedioate (1:1)	133-135
20	N-[(3,3-diphenyl)propyl]-2-iodo-5- methoxy-N,α-dimethylbenzeneethanamine	oil

Example 52

25 N-[2-(2,6-Dichlorophenyl)ethyl]-2-iodo 5-methoxy-α-
methylbenzeneethanamine E-2-Butenedioate 1:1

A solution of 8.0g (27.6 mmole) of 2-iodo-5-methoxyphenyl-2 propanone, 5.5g (29.0 mmole) of 2,6-dichlorophenyethylamine and 52mg (0.28 mmole) p-toluenesulfonic acid in 100 ml toluene was heated under reflux with azeotropic removal of water. After four hours the solvent was evaporated in vacuo. The crude imine was dissolved in 100 ml MeOH and 1.4g (22.1mmole) of sodium cyanoborohydride was added. The mixture was stirred for 20 hr. A methanolic hydrogen chloride solution was added to bring the pH to 1. The mixture was stirred for 30 min. The solvent was evaporated in vacuo. The residue was partitioned between

ether and 3N NaOH solution. The ether layer was washed with brine, dried and the solvent was evaporated in vacuo. The residue was combined with 3.0g of fumaric acid in 2-propanol. The precipitated solid was collected to give
 5 10.8g of the title compound as a white solid, mp 172-175°C.

Example 53

10 Using the procedure of Example 52 and employing equivalent quantities of the appropriate amine in place of 2,6-dichlorophenethylamine and 2-iodo 5-methoxyphenyl-2-propanone or the appropriate ketone, there were obtained as products respectively:

15

	<u>mp°C</u>
α -[[2-(2-Iodo-5-methoxyphenyl)-1-methylethyl]amino]-methylbenzenemethanol Hydrochloride	162-168

20

2-Iodo-5-methoxy- α -methyl-N-[2-(4-nitrophenyl)-ethyl]benzeneethanamine E-2-Butenedioate	150-160
--	---------

N-[2-(4-Chlorophenyl)ethyl]-2-iodo-5-methoxy- α -methylbenzeneethanamine

25

N-[2-(2-Iodo-5-methoxyphenyl)-1-methylethyl]-2-naphthaleneethanamine ethanedioate	167-169
---	---------

30

2-Iodo-5-methoxy-N-(2-phenoxyethyl)-benzenepropanamine ethandioate	167-169
--	---------

2-Iodo-5-methoxy- α -methyl-N-(2-phenylethyl)-benzeneethanamine

35

N-[2-(2,6-Dichlorophenyl)ethyl]-2-iodo-5-methoxy- α -methylbenzenepropanamine

N-[2-(3,5-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxy- α -methylbenzenepropanamine Hydrochloride 133-136

5 N-[2-(3,4-dimethoxyphenyl)ethyl]-5-(dimethyl-amino)-2-iodo- α -methylbenzenepropanamine ethanedioate 138-142

Example 54

10 N-[2-(3-Chlorophenyl)ethyl]-2-iodo-5-methoxy- α -methylbenzeneethanamine Ethanedioate

15 A solution of 30.0g (0.10 mole) 2-iodo-5-methoxyphenyl-2-propanone, 16.1g (0.10 mole) of m-chlorophenethylamine and 0.2g (0.10 mmole) of p-toluenesulfonic acid in 200 ml of toluene was heated under reflux with azeotropic removal of water for 16 hr. The solvent was evaporated in vacuo. The residue (crude imine) was taken up in 100 ml of MeOH and 3.9g (0.10 mole) of sodium borohydride pellets were
20 added. After 3 hr an additional 0.89g (0.023 mole) of sodium borohydride was added. The mixture was stirred for 16 hr. A 5 ml sample of glacial acetic acid was added. After bubbling ceased, the mixture was partitioned between CH_2Cl_2 and 3N NaOH solution. The organic layer was dried
25 (K_2CO_3) and the solvent was evaporated in vacuo. The residue was combined with 10.1g of oxalic acid in boiling MeOH. The solid was collected to give the title compound or a white crystalline solid, mp 194-197 (38g, 87% yield).

30

Example 55

Using the procedure of Example 54 and employing an equivalent quantity of the appropriate amine in place of
35 m-chlorophenethylamine there were obtained as products respectively:

		<u>mp °C</u>
	2-Iodo-5-methoxy-N-[2-(2-methoxyphenyl)ethyl]- α -methylbenzeneethanamine Ethanedioate	167-169.5°C
5	N-[2-(2,5-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxy- α -methylbenzeneethanamine Ethanedioate	115-117°C
10	N-[2-(3,5-Dichlorophenyl)ethyl]-2-iodo-5-methoxy- α -methyl benzenethanamine (E)-2-butenedioate	185-187°C

Example 56

Using the procedure of Example 39 and employing the appropriate secondary amine from Examples 52 to 55 and formaldehyde or the appropriate aldehyde there were obtained as products respectively:

		<u>mp °C</u>
20	N-Butyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy- α -methylbenzeneethanamine	
25	2-Iodo-5-methoxy-N, α -dimethyl-N-[2-(phenyl)-ethyl]benzeneethamine Ethanedioate	163-165
	N-[2-(2,6-Dichlorophenyl)ethyl]-2-iodo-5-methoxy N, α -dimethylbenzeneethanamine Perchlorate	160-163
30	N-[2-(2,6-Dichlorophenyl)ethyl]-2-iodo-5-methoxy N, α -dimethylbenzenepropanamine	
	N-[2-(3-Chlorophenyl)ethyl]-2-iodo-5-methoxy N, α -dimethylbenzeneethanamine Ethanedioate	175-178
35	N-[2-(2,5-Dimethoxyphenyl)ethyl]-2-iodo-5-methoxy-N, α -dimethylbenzeneethanamine Ethanedioate	134-137

N-[2-(3,4-Dimethoxyphenyl)ethyl-5-dimethylamino-2-iodo-N, α -dimethylbenzenepropanamine Ethanedioate 172-173

EXAMPLE 57

5

Using the procedure of Example 49 and employing an equivalent quantity of the appropriate iodoamine from Examples 51-56 in place of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-iodo-5-methoxy N, α -dimethylbenzeneethanamine and an equivalent quantity of phenylacetylene in place of p-trifluoromethylphenylacetylene there were obtained as products respectively:

15	N-[3,3-(diphenyl)propyl]-2-methoxy-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedionate	<u>mp °C</u> 160-162
20	N-[2-(2,6-Dichlorophenyl)ethyl]-5-methoxy- α -methyl-2-(phenylethynyl)benzeneethanamine Hydrochloride	169-171
25	α -[[[2-[5-Methoxy-2-(phenylethynyl)phenyl]-1-methylethyl]amino]methyl]benzenemethanol (E)-2-Butenedioate (2:1)	168-169
30	N-Butyl-N-2-(3,4-dimethoxyphenyl)ethyl]-5-methoxy- α -methyl-2-(phenylethynyl)-benzeneethanamine	oil
	N-[2-(3,4-Dimethoxyphenyl)ethyl]-5-(dimethylamino)-N, α -dimethyl-2-(phenylethynyl)benzene-propanamine Hydrochloride Hydrate (100:200:127)	162-164

	5-Methoxy- α -methyl-N-[2-(4-nitrophenyl)ethyl]- 2-(phenylethynyl)benzeneethanamine (E)- 2-Butenedioate (2:1)	155-157
5	N-2-(4-Chlorophenyl)ethyl]-5-methoxy- α -methyl-2- (phenylethynyl)benzeneethanamine (E)-2-Butenedioate Hydrate (100:75:14)	162-164
10	N-[2-[5-Methoxy-2-(phenylethynyl)phenyl]-1- methylethyl]-N-methyl-2-naphthaleneethanamine Hydrochloride Hydrate (25:25:9)	135-137
15	5-Methoxy- α -methyl-N-(2-phenoxyethyl)-2-(phenyl- ethynyl)benzenepropanamine (E)-2-Butenedioate (2:1)	78-79
20	N-[2-(2,6-Dichlorophenyl)ethyl]-5-methoxy- α - methyl-2-(phenylethynyl)benzenepropanamine Hydrochloride	156-159
	5-Methoxy-N, α -dimethyl-N-(2-phenylethyl)-2-(phenyl- ethynyl)benzeneethanamine Hydrochloride (1:1)	150-151
25	N-[2-(2,6-Dichlorophenyl)ethyl]-5-methoxy-N, α - dimethyl-2-(phenylethynyl)benzenepropanamine (E)-2-Butenedioate (1:1)	131-134
30	N-[2-(3-Chlorophenyl)ethyl]-5-methoxy- α -methyl- 2-(phenylethynyl)benzeneethanamine Hydrochloride	178-179
	N-[2-(2-Methoxyphenyl)ethyl]-5-methoxy- N, α -dimethyl-2-(phenylethynyl)benzeneethanamine Hydrochloride	165-166

- N-[2-(3-Chlorophenyl)ethyl]-5-methoxy-N, α -dimethyl-
2-(phenylethynyl)benzeneethanamine Hydrochloride Hydrate
(2:2:1) 83-88
- 5 N-[2-(2,5-Dimethoxyphenyl)ethyl]-5-methoxy- α -methyl-
2-(phenylethynyl)benzeneethanamine Hydrochloride
2-Propanolate (4:4:1) 143-145
- 10 N-[2-(2,5-Dimethoxyphenyl)ethyl]-5-methoxy-N, α -
dimethyl-2-(phenylethynyl)benzeneethanamine
(E)-2-Butenedioate (1:1) 139-140
- 15 N-[2-(3,5-Dimethoxyphenyl)ethyl]-5-methoxy-
 α -methyl-2-(phenylethynyl)benzenepropanamine
Hydrochloride 144-146
- 20 2-[[2-(3,4-Dichlorophenyl)ethyl][2-[5-methoxy-
2-(phenylethynyl)phenyl]-1-methylethyl]
amino]ethanol Hydrochloride (1:1) 113-115
- 5-Methoxy- α -methyl-N,N-bis (2-phenylethyl)-2-(phenyl-
ethynyl)benzenepropanamine oil
- 25 Anal. Calc'd. for $C_{35}H_{37}NO$: C 86.20; H, 7.65; N, 2.87
Found: C 86.07; H, 7.65; N, 2.72
- 30 N-[2-(3,5-Dichlorophenyl)ethyl]-5-methoxy- α -methyl-
2-(phenylethynyl)benzeneethanamine (E)-2-
Butenedioate 186-187
- N-[2-(3,5-Dichlorophenyl)ethyl]-5-methoxy N, α -dimethyl-
2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate

Example 58

35

Using the procedure of Example 36 and employing an
equivalent quantity of the iodoamines from Example 51 in

place of 2-iodo 5-methoxy-N, α -dimethyl-N-[4-(phenyl)butyl
benzeneethanamine there were obtained as products,
respectively:

	<u>mp °C</u>
5	
N-[2-(3,4-Dichlorophenyl)ethyl]-5-methoxy-N, α - dimethyl-2-(phenylethynyl)benzenepropanamine Hydrochloride Hydrate (4:4:1)	107-108
10	
5-Methoxy-N, α -dimethyl-2-phenyl-ethynyl-N-[3-(phenyl) propyl]benzeneethanamine Hydrochloride	204-205

Example 59

15

N-[2-(3,5-Dimethoxyphenyl)ethyl]-5-methoxy- α -methyl-2-
(phenylethynyl)benzeneethanamine (E)-2-Butenedioate 2:1

20 A 60g sample of 5A molecular sieves was suspended in 100ml
of toluene and 8.5g (32 mmole) of 5-methoxy-2-(phenyl-
ethynyl)-2-propanone and 5.82g (32 mmole) of 3,5-di-
methoxyphenethylamine were added. The mixture was stirred
for two days at room temperature. The sieves were filter-
ed and washed with toluene. The solvent was evaporated
25 in vacuo. The residue was taken up in 50 ml of MeOH and
0.4g (10.6 mmole) of sodium borohydride (pellet) was
added. After 90 min water was added. The mixture was
partitioned between CH₂Cl₂ and water. The organic
solution was washed with diluted hydrochloric acid. NaOH
30 solution and water. The solution was dried (K₂CO₃) and
the solvent water evaporated in vacuo. The residue was
taken up in MeOH and 2.76g fumaric acid added. The solid
(9.14g, 63% yield) was collected and dried to give the
title compound as a white solid mp 185-190°C
35 (decomposition).

Example 60

Using the procedure of Example 59 and employing an equivalent quantity of the appropriate amine in place of 3,5-dimethoxyphenethylamine there were obtained as products respectively:

		<u>mp °C</u>
10	N-[2-(2-Chlorophenyl)ethyl]-5-methoxy- α -methyl-2-(phenylethynyl)benzeneethanamine Hydrochloride (1:1)	158-159
15	5-Methoxy-N-[2-(3-trifluoromethylphenyl)ethyl]- α -methyl-2-(phenylethynyl)benzeneethanamine Hydrochloride (1:1)	164-166
20	5-Methoxy-N-[2-(3-methoxyphenyl)ethyl]- α -methyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate (2:1)	154-156
25	N-[2-(2,3-Dimethoxyphenyl)ethyl]-5-methoxy- α -methyl-2-(phenylethynyl)benzeneethanamine Hydrochloride	162-163

Example 61

Using the procedure of Example 39 and employing an equivalent quantity of the appropriate amine from Examples 57 and 59 in place of N-[2-(3,4-dimethoxyphenyl)ethyl]-5-methoxy-N-methyl-2-(phenylethynyl)benzeneethanamine, there were obtained as products respectively:

		<u>mp °C</u>
35	5-Methoxy-N-[2-(3-methoxyphenyl)ethyl]-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine Hydrochloride (1:1)	150-151

-62-

- N-2-(2,3-Dimethoxyphenyl)ethyl]-5-methoxy N, α -dimethyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate (1:1) 131-133
- 5 N-[2-(3,5-Dimethoxyphenyl)ethyl]-5-methoxy-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine Hydrochloride Hydrate (16:16:1) 165-166
- 10 N-[2-(2-Chlorophenyl)ethyl]-5-methoxy-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate (1:1) 136-139
- 15 5-Methoxy-N-[2-(3-trifluoromethylphenyl)ethyl]-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate (1:1) 130-132
- 20 N-[2-(3,5-Dimethoxyphenyl)ethyl]-5-methoxy-N, α -dimethyl-2-(phenylethynyl)benzenepropanamine (E)-2-Butenedioate (1:1) 127-129
- N-[2-(3,5-Dichlorophenyl)ethyl]-5-methoxy-N, α -dimethyl-2-(phenylethynyl)benzeneethanamine (E)-2-Butenedioate (1:1) 136-8
- 25 Example 62
- [[2-(3,4-Dichlorophenyl)ethyl][2-[2-iodo-5-methoxy-phenyl]-1-methylethyl]amine]ethanol (E)-2-Butenedioate
- 30 A sample (1.3g) of ethylene oxide was condensed in a pressure bottle at -68° and a cold solution of 4.2g of N-[2-(3,4-dichlorophenyl)ethyl]-2-iodo-5-methoxy- α -methylbenzeneethanamine in 8 ml of MeOH was added. The bottle was sealed and heated on a steam bath overnight. A 1.0g
- 35 sample of fumaric acid was added. The solid was collected

to give 3.3g (60% yield) of the title compound as white crystals mp 133-140°C.

Example 63

5

4-(3-Dimethylaminophenyl)-3-butene-2-one

Using the procedure of Example 12 and employing an equivalent quantity of 3-dimethylaminobenzaldehyde in place of 3-methoxybenzaldehyde the title compound was obtained as a yellow solid, mp 47-49°C.

Example 64

15 4-(3-Dimethylaminophenyl)-2-butanone Ethanedioate

A 103 ml (0.38 mole) sample of tri-n-butyltin hydride was added dropwise over 15 min to a solution of 60.4g (0.319 mole) of 4-(3-dimethylaminophenyl)-3-butene-2-one, 19.15 ml of glacial acetic acid and 3.7g (0.032 mole) of tetrakis(triphenylphosphine)palladium (0) in 900 ml of dry toluene under N₂. The mixture was stirred for two hours, A 600 ml sample of 3N HCl was added and the mixture was stirred one hour. The acid layer was separated and the toluene layer was extracted three times with 3N HCl. The combined HCl solutions were made basic with NaOH solution. The mixture was extracted with ether. The ether was washed with brine and dried (K₂CO₃). The solvent was evaporated in vacuo. An oxalate salt was prepared from MeOH. There was obtained 67.5g (75% yield) of the title compound as a solid mp 108-110°C.

Example 654-(5-Dimethylamino-2-iodophenyl)-2-butanone Hydrochloride

5 A solution of 0.16 moles of iodonium nitrate in 280 ml of
CHCl₃ was added to 30.4g of 4-(3-dimethylaminophenyl)-2-
butanone. The mixture was stirred for 2 hr. Ether was
added and the precipitated solid was removed by filtra-
10 tion. The solvent was evaporated in vacuo. The residue
was partitioned between water and ether. The ether
solution was washed with sodium thiosulfate solution and
brine. The solution was dried (K₂CO₃) and the solvent
evaporated. The residue was taken up in ether and
15 ethereal hydrogen chloride added. The precipitate (47.4g,
85% yield) of the title compound was collected mp 120-
121°C.

Example 6620 2-Iodo-5-methoxy- α -methylbenzenepropanamine

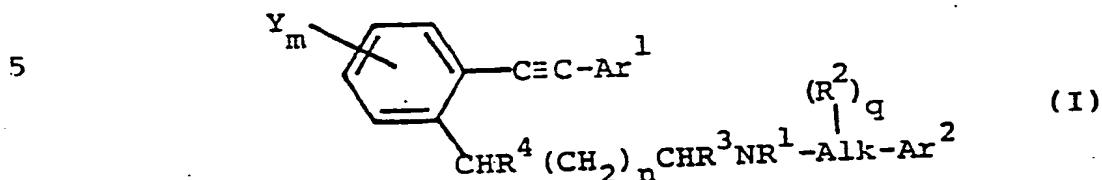
A sample of 2.9g (4.6 mmole) of sodium cyanoborohydride
was added to a suspension of 50.7g (0.66 mole) of ammonium
acetate and 20.0g (66 mmole) of 4-(2-iodo-5-
25 methoxyphenyl)-2 butanone in 300 ml of MeOH. The mixture
was stirred for 5.5 hr. Concentrated HCl solution was
added to bring the pH to 1. The mixture was stirred for
16 hr. The MeOH was evaporated in vacuo, and the residue
was partitioned between NaOH solution and ether. The
30 organic solution was washed with brine, dried (K₂CO₃) and
the solvent evaporated in vacuo to give 20.1 g of a yellow
oil. The oil was combined with 7.64g of fumaric acid in
boiling 2-propanol. The solution was cooled and the
crystals of title compound, were collected.

Example 672-Iodo-5-methoxy-N,N-bis(2-phenylethyl)benzenepropanamine

- 5 A sample of 3.7g (59 mmole) of sodium cyanoborohydride was added to a solution of 6.0g (19.7 mmole) of 2 iodo-5-methoxy- α -methylbenzenepropanamine and 14.2 ml (0.12 mole) of phenylacetaldehyde in 60 ml of MeOH. Methanolic hydrogen chloride was added dropwise. After 16 hr the
- 10 mixture was made frankly acidic by addition of methanolic hydrogen chloride. The mixture was stirred for one hour. The MeOH was evaporated in vacuo and the residue partitioned between ether and NaOH solution. The ether was evaporated in vacuo. The residue was redissolved in
- 15 ether and ethereal hydrogen chloride added. The ether was decanted from the precipitated gum and the gum washed twice with ether. The gum was partitioned between NaOH solution and ether. The ether was washed with brine, dried and the solvent evaporated in vacuo. The volatile
- 20 by products were removed by heating the residue up to 125°C at 0.005 mm Hg in a Kugelrohr. The pot residue contained 9.1 g 26% yield of the title compound as a pale yellow oil.

CLAIMS

1. An acetylene derivative of the following formula (I):



wherein

- 10 Y is independently alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyloxy, alkanoylamino, amino, monoalkylamino, dialkylamino, hydroxy, halogen or cyano or methylenedioxy or ethylenedioxy at adjacent ring carbons;

15

m is 0, 1, 2 or 3;

- Ar¹ is phenyl or a 5- or 6-membered heterocyclic aromatic ring which rings may be independently substituted by one or more of alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino, dialkylamino, carboxamido, halogen, fluoroalkyl or cyano;
- 20

- 25 R¹ is hydrogen, alkyl, hydroxyalkyl, cycloalkyl or cycloalkylalkyl, or R¹ is independently selected from the group consisting of the defined values of -Alk-Ar²;

30

R² is independently hydroxy, alkyl or phenyl;

Alk is straight chain alkylene of about 1 to 4 carbons;

35

q is 0, 1 or 2 or 3 if Alk is alkylene of about 2 to 4 carbons;

Ar² is a phenyl, phenoxy, thiophenoxy, naphthyl or a
5- or 6-membered heterocyclic aromatic ring which
rings may be substituted independently by one or
more of alkyl, alkoxy, alkylthio, hydroxy, halogen,
5 fluoroalkyl, nitro, amino or dialkylamino or by
methylenedioxy at adjacent ring carbons;

R³ is hydrogen, alkyl or alkoxyalkyl;

10 n is 0, 1 or 2; and

R⁴ is hydrogen or alkyl,

and the pharmaceutically acceptable acid addition salts
15 and quarternary ammonium compounds thereof.

2. The acetylene of Claim 1,

wherein

20

Y is alkyl of about 1 to 6 carbons; alkoxy of about 1
to 6 carbons; alkylthio of about 1 to 6 carbons;
alkylsulfinyl of about 1 to 6 carbons; alkylsulfonyl
of about 1 to 6 carbons; alkanoyloxy of about 2 to 6
25 carbons; alkanoylamino of about 2 to 6 carbons;
amino; monoalkylamino of about 1 to 6 carbons;
dialkylamino of about 2 to 12 carbons; hydroxy;
fluoro, chloro or bromo; cyano; or methylenedioxy or
ethylenedioxy;

30

m is 0, 1, 2 or 3;

- Ar¹ is phenyl or a 5- or 6-membered heterocyclic aromatic ring containing 1,2 or 3 nitrogen, sulphur or oxygen atoms which rings may be substituted with one or more of alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl or alkylamino of about 1 to 6 carbons each, amino, dialkylamino of about 2 to 12 carbons, carboxamido, fluoro, chloro or bromo, fluoroalkyl of about 1 to 6 carbons or cyano;
- R¹ is hydrogen, alkyl of about 1 to 6 carbons, hydroxyalkyl of about 1 to 6 carbons, cycloalkyl of about 3 to 6 carbons or cycloalkylalkyl of about 4 to 7 carbons or R¹ is independently a value of -Alk-Ar²;
- R² is hydroxy, alkyl of about 1 to 4 carbons or phenyl;
- q is 0, 1 or 2;
- Alk is methylene, ethylene, trimethylene or tetramethylene;
- Ar² is phenyl, phenoxy, thiophenoxy, naphthyl or a 5- or 6-membered heterocyclic aromatic ring having one nitrogen, sulfur or oxygen atom which rings may be substituted by one or more of alkyl, alkoxy or alkylthio of about 1 to 6 carbons each, hydroxy, fluoro, chloro, bromo, fluoroalkyl of about 1 to 6 carbons, nitro, amino, dialkylamino of about 2 to 12 carbons or methylene dioxy;
- R³ is hydrogen, alkyl of about 1 to 6 carbons or alkoxyalkyl of about 1 to 6 carbons in each alkyl portion;
- n is 0, 1 or 2; and
- R⁴ is hydrogen or alkyl of about 1 to 6 carbons.

3. The acetylene of Claim 1, wherein

5 Y is independently alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkanoyloxy, alkanoylamino, amino, monoalkylamino, dialkylamino, hydroxy, halogen or cyano or methylenedioxy or ethylenedioxy at adjacent ring carbons;

10 m is 0, 1, 2 or 3;

15 Ar¹ is phenyl or a 5- or 6-membered heterocyclic aromatic ring which rings may be independently substituted by one or more of alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxamido, halogen, fluoroalkyl or cyano;

R¹ is hydrogen, alkyl, cycloalkyl or cycloalkylalkyl;

20 R² is alkyl;

Alk is straight chain alkylene of about 1 to 4 carbons;

25 q is 0, 1 or 2 or 3 if Alk is alkylene of about 2 to 4 carbons;

30 Ar² is a phenyl, phenoxy, thiophenoxy or a 5- or 6-membered heterocyclic aromatic ring which rings may be substituted independently by one or more of alkyl, alkoxy, alkylthio, hydroxy, halogen, fluoroalkyl, amino or dialkylamino or by methylenedioxy at adjacent ring carbons;

35 R³ is hydrogen, alkyl or alkoxyalkyl;

n is 0, 1 or 2; and

R⁴ is hydrogen or alkyl,

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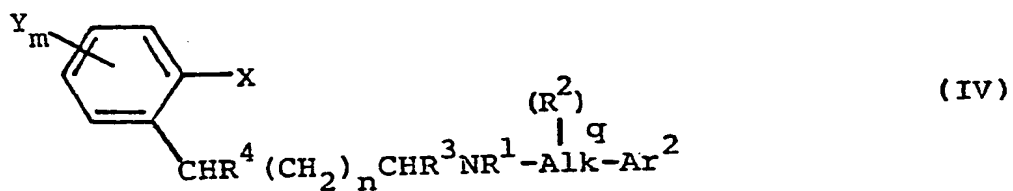
and the pharmaceutically acceptably acid addition salts and quarternary ammonium compounds thereof.

4. The acetylene of any one of claims 1 to 3 wherein Ar¹ is phenyl or substituted phenyl and Ar² is phenyl or substituted phenyl.
5. the acetylene of any one of claims 1 to 4 wherein Alk is methylene or ethylene and n is 0 or 1.
6. The acetylene of any one of claims 1 to 5 wherein Y is alkoxy; m is 0 or 1; Ar is phenyl or phenyl substituted with one or more substituents; R¹ is hydrogen or alkyl; R² is alkyl; q is 0 or 1; Alk is methylene or ethylene; Ar² is phenyl or phenyl with at least one substituent; R³ is hydrogen or alkyl; n is 0 or 1; and R⁴ is hydrogen.
7. The acetylene of any one of claims 1 to 6 wherein Y is alkoxy and m is 1.
8. The acetylene of any one of claims 1 to 7 wherein Y is methoxy at the position para to the acetylene moiety; m is 1; Ar¹ is phenyl; R¹ is methyl; q is 0, Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; R³ is methyl; n is 1; and R⁴ is hydrogen.
9. The acetylene of any one of claims 1 to 7 wherein Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is methyl; q is 0; Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; R³ is hydrogen; n is 0; and R⁴ is hydrogen.
10. The acetylene of any one of claims 1 to 7 wherein Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is hydrogen; q is 0; Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; n is 0; and R⁴ is hydrogen.
11. The acetylene of any one of claims 1 to 7 wherein Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is methyl; q is 0; Alk is ethylene; Ar² is 3,4-dimethoxyphenyl; R³ is methyl; n is 0; and R⁴ is hydrogen.

12. The acetylene of any one of claims 1 to 7 wherein Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is hydrogen; q is 0; Alk is ethylene; Ar² is 3,4-dichlorophenyl; n is 0; and R⁴ is hydrogen.
13. The acetylene of any one of claims 1 to 7 wherein Y is methoxy at the position para to the acetylene; m is 1; Ar¹ is phenyl; R¹ is methyl; q is 0; Alk is ethylene; Ar² is 3,4-dichlorophenyl; R³ is hydrogen; n is 0; and R⁴ is hydrogen.
14. The acetylene of any one of claims 1 to 3 wherein said heterocyclic ring for Ar¹ is selected from the group consisting of a thiophene, pyrrole, furan, pyrazole, imidazole, triazole, oxazole, thiazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine or thiazine ring and said heterocyclic ring for Ar² is selected from the group consisting of a furan, thiophene, pyrrole or pyridine ring.
15. The acetylene of any one of claims 1 to 14 wherein said pharmaceutically acceptable acid addition salts are formed from acids selected from the group consisting of hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, fumaric, maleic, cyclohexylsulfamic, citric, lactic and methanesulfonic and said quaternary ammonium compounds are those formed with an alkylhalide or alkylsulfate.
16. A pharmaceutical composition comprising an acetylene of any one of claims 1 to 15 in combination with a pharmaceutically acceptable diluent or carrier.
17. An acetylene of any one of claims 1 to 15 or a composition of claim 16 for use in treating angina pectoris.
18. An acetylene of any one of claims 1 to 15 or a composition of claim 16 for treating hypertension.

19. An acetylene of any one of claims 1 to 15 or a composition of claim 16 for treating cardiac arrhythmias.

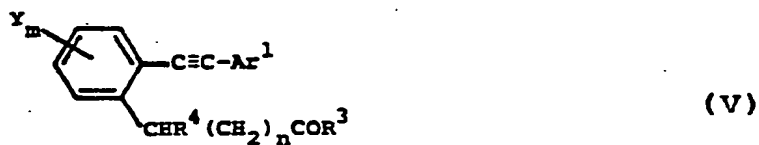
20. An amine of the following formula (IV):



wherein Y, m, R¹, R², Alk, q, Ar², R³, n, and R⁴ are as defined in claim 1 and X is a halogen atom.

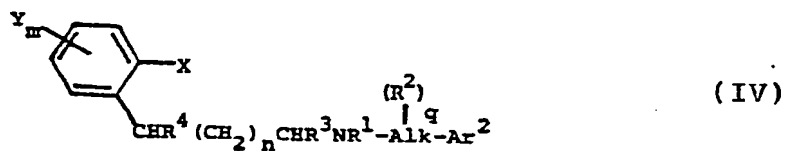
21. A process for the preparation of an acetylene of formula (I) of Claim 1, which comprises:

10 a) reductively alkylating an amine of formula R¹NH-Alk(R²)_q-Ar² with a compound of the following formula (V):



or

b) coupling an arylhalide of the following formula (IV):



wherein X is a halogen, with an Ar^1 -acetylene.

22. A process for the production of a composition according to claim 16 comprising admixing an acetylene of any one of claims 1 to 15 with a pharmaceutically acceptable diluent or carrier.

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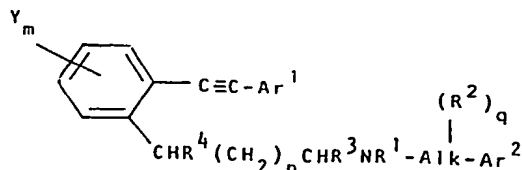
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(54) Arylalkyl (arylethynyl) aralkyl amines for use as vasodilators and antihypertensives.

(57) Acetylenes of the formula (I):



wherein Y, m, R¹, R², q, Alk, R³, n and R⁴ are as defined herein and Ar¹ and Ar² are aromatic, including the salts and ammonium derivatives of formula (I), in treating angina, hypertension and cardiac arrhythmias. Pharmaceutical compositions, methods of use and synthesis and novel intermediates are also part of the invention.



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EUROPEAN SEARCH REPORT

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Place of search THE HAGUE		Date of completion of the search 26-08-1986	Examiner MOREAU J.M.
CATEGORY OF CITED DOCUMENTS			
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